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Ato nuk kanë nevojë për aprovimin tuaj*...

Vetëm për sigurinë tuaj.



Gjeni rehati në mbrojtjen dhe përshtatshmërinë e nevojshme për pacientët tuaj të moshuar me fibrilacion atrial.[1-3]

*Miratimi në këtë rast lidhet me stilet e tyre të jetesës.



PËRMBLEDHJE E KARAKTERISTIKAVE TË PRODUKTIT

EMRI I PRODUKTIT MJEKËSOR
Roteas 15 mg tableta të veshura me film Roteas 30 mg tableta të veshura me film Roteas 60 mg tableta të veshura me film
PËRBËRJA SASIORE DHE SASIORE
Çdo tabletë e veshur me film përmban edoksaban (në trajtën e edoksaban tosilat).
FORMA FARMACEUTIKE
Tableta të veshura me film.
VEÇORITË KLINIKE
Indikimet terapeutike
Roteas indikohet për parandalimin e insultit cerebral (goditjes në tru) dhe embolisë sistemike në pacientët e rritur me fibrilacion atrial jovalvular (NVAF) me një ose më shumë faktorë rreziku, të tillë si insuficienca kardiake kongjestive hipertensioni, mosha ≥75 vjeç, diabeti mellit, insulti cerebral ose sulmi iskemik tranzitor (TIA) i mëparshëm. Roteas indikohet për trajtimin e trombozës së venave të thella (DVT) dhe embolisë pulmonare (PE), dhe për parandalimin e DVT dhe PE rekurente tek të rriturit.
Dozimi dhe mënyra e përdorimit
Dozimi
Parandalimi i insultit cerebral dhe embolisë sistemike Doza e këshilluar është 60 mg edoksaban një herë në ditë. Terapia me edoksaban në pacientët me NVAF duhet të vazhdojë për një kohë të gjatë. Trajtimi i DVT, trajtimi i PE dhe parandalimi i DVT dhe PE (VTE) rekurente
Doza e këshilluar është 60 mg edoksaban një herë në ditë pas përdorimit fillestar të një antikoagulanti parenteral për të paktën 5 ditë. Edoksaban dhe antikoagulanti parenteral fillestar nuk duhet të administrohen njëkohësisht. Kohëzgjatja e terapisë për trajtimin e DVT dhe PE
(tromboembolisë venoze (VTE)) dhe parandalimin e VTE rekurente duhet të individualizohet pas një vlerësimi të kujdesshëm të përfitimit të trajtimit përkundrejt rrezikut për gjakderdhje. Kohëzgjatja e shkurtër e terapisë (të paktën 3 muaj) duhet të bazohet në faktorë të rrezikut të përkohshëm (p.sh. ndërhyrje kirurgjikale, trauma, imobilizim në kohë e fundit), ndërsa kohëzgjatjet më të gjata duhet të bazohen në faktorë të rrezikut të përhershëm ose në DVT apo PE idiopatike. Për NVAF dhe VTE, doza e këshilluar është 30 mg edoksaban një herë në ditë tek pacientët me një ose më shumë nga faktorët klinikë të mëposhtëm:
- Dëmtim renal i formës së mesme ose të rëndë (klirensi i kreatininës (CrCl) 15 - 50 mL/min)
- Peshë trupore e ulet ≤ 60 kg
- Përdorimi i njëkohshëm i frenueseve të mëposhtëm të P-glikoproteinës (P-gp): ciklosporinë, dronedaron, eritromicinë ose ketokonazol.

Doza e harruar Në rast se harrohet një dozë edoksaban, doza duhet të merret menjëherë dhe më pas të vazhdohet ditën tjetër me marrjen një herë në ditë siç këshillohet. Pacienti nuk duhet të marrë dyfishin e dozës së përshkruar në të njëjtën ditë për të kompensuar dozën e harruar.
Kalimi nga barnat e tjerë në edoksaban dhe anasjelltas Terapia e vazhdueshme me antikoagulantë në pacientët me NVAF dhe VTE është e rëndësishme. Megjithatë, mund të ketë situata që kërkojnë një ndryshim në terapinë antikoaguluese.
Popullimi në ekstrazyrë Popullata e moshuar Nuk nevojitet ndonjë pakësim i dozës.
Dëmtimi i funksionit të veshikave Funksioni i veshikave duhet të vlerësohet në të gjithë pacientët duke llogaritur CrCl para fillimit të trajtimit me edoksaban me qëllim që të përjashtohen pacientët me sëmundje renale në stadin përfundimtar (p.sh. CrCl <15 mL/min), të përdoret doza e saktë e edoksaban në pacientë me CrCl 15 - 50 mL/min (30 mg një herë në ditë), në pacientët me CrCl > 50 mL/min (60 mg një herë në ditë) dhe kur vendoset që edoksaban të përdoret në pacientët me CrCl të shtuar. Funksioni i veshikave gjithashtu duhet të vlerësohet kur dyshohet ndonjë ndryshim në funksionin renal gjatë trajtimit (p.sh. në rast të hipovolemisë, dehidratimit dhe të përdorimit të njëkohshëm të disa produkteve mjekësore). *Dëmtimi i funksionit të mëlçisë* Edoksaban është e kundërindikuar në pacientët me sëmundje të mëlçisë të shoqëruara me koagulopati dhe rrezik
për hemorragji klinikisht të rëndësishme. Në pacientët me dëmtim hepatik të rëndë përdorimi i edoksaban nuk është i këshillueshëm. Në pacientët me dëmtim të hepatik të formës së lehtë ose të mesme doza e këshilluar është 60 mg edoksaban një herë në ditë. Në pacientët me dëmtim të hepatik të formës së lehtë ose të mesme edoksaban duhet të përdoren me kujdes.
Pesha trupore Për pacientët me peshë trupore ≤ 60 kg, doza e këshilluar është 30 mg edoksaban një herë në ditë. *Gjinia* Nuk nevojitet ndonjë pakësim i dozës.
Përdorimi i njëkohshëm i Roteas me inhibitorët e P-glikoproteinës (P-gp) Në pacientët që marrin njëkohësisht Roteas dhe inhibitorët e
mëposhtëm të P-gp: ciklosporinë, dronedaron, eritromicinë, ose ketokonazol, doza e këshilluar është 30 mg Roteas një herë në ditë. Nuk nevojitet ndonjë pakësim i dozës gjatë përdorimit të njëkohshëm me amiodaron, kinidinë ose verapamil.
Përdorimi i Roteas me inhibitorë të tjerë të P-gp, përfshirë inhibitorët e proteazës së HIV, nuk është studiuar.
Pacientët që i nënshtrohen kardioversionit Roteas mund të fillohet ose të vazhdohet në pacientët që mund të kenë nevojë për kardioversion. Për kardioversionin e drejtuar nga ekokardiograma transoezofageale (TEE) në pacientët që nuk janë trajtuar më parë me antikoagulantë, trajtimi me Roteas duhet të fillohet të paktën **2 orë** përpara kardioversionit për të siguruar një antikoagulim adekuat. Kardioversioni duhet të bëhet jo më vonë se 12 orë pas marrjes së dozës së Roteas në ditën e procedurës. **Për të gjithë pacientët që i nënshtrohen kardioversionit:** Përpara kardioversionit duhet të kërkohet konfirmimi që pacienti ka marrë Roteas siç është përshkruar. Vendimi për fillimin e trajtimit dhe kohëzgjatjen e tij duhet të jenë në përputhje me udhëzimet e përcaktuara për trajtimin me antikoagulantë te pacientëve që i nënshtrohen kardioversionit.
Popullata pediatrike Edoksaban nuk rekomandohet për përdorim tek fëmijët dhe adoleshentët nga lindja deri në 18 vjeç me ngjarje të
konfirmuara të VTE (PE dhe/ose DVT) pasi efikasiteti nuk është vërtetuar. *Metoda e administrimit* Përdorimi nga goja. **Edoksaban mund të merret njëkohësisht me ushqimin ose pavarësisht prej tij.** Për pacientët që nuk mund ta gëlltisin tabletën e plotë, Roteas mund të shtypet apo thërrmohet, të përzihet me ujë ose pure molle dhe të merret menjëherë nga goja. Një tjetër mënyrë është që tabletat të thërrmohen dhe të treten në një sasi të vogël uji dhe të jepen menjëherë nëpërmjet një tubi gastrik ose ushqyerës gastrik, e pas kësaj duhet të lahet me ujë. Tabletat e thërrmuara Roteas mund të qëndrojnë në ujë ose pure molle deri në 4 orë.
Kundërindikimet
Mbindjeshmëria ndaj lëndës vepruese ose ndaj ndonjë prej lëndëve të tjera përbërëse (ekscipientëve). Hemorragji aktive klinikisht e rëndësishme. Sëmundja hepatike të shoqëruara me koagulopati dhe rrezik për gjakderdhje klinikisht të rëndësishme. Gjendje ose lezione, në rastet kur konsiderohen se janë një rrezik i rëndësishëm për gjakderdhje madhore. Këto mund të përfshijnë ulceracionet gastrointestinale aktuale ose të ndodhura kohët e fundit, neoplazitë malinje me rrezik të lartë për gjakderdhje, dëmtimet e trurit ose të palcës kurrizore të ndodhura kohët e fundit, ndërhyrjet kirurgjikale në tru, palcës kurrizore ose sy të kryera kohët e fundit, hemorragjinë intrakraniale të pësuar kohët e fundit, varicet ezofageale të njohura ose të dyshuara, keqformimet arteriovenoze, aneurizmat vaskulare ose anomalitë vaskulare madhore intraspinale ose intracerebrale. Hipertensioni i rëndë i pakontrolluar. Trajtim shoqërues me ndonjë antikoagulant tjetër, p.sh. heparinë e pafraksionuar (UFH), heparina me peshë të ulët molekulare (enoksaparinë, dalteparinë, etj.), derivate të heparinës (fondaparinux, etj.), antikoagulantë oralë (warfarinë, dabigatran eteksilat, rivaroksaban, apiksaban etj), përveç rregullimeve specifike të ndryshimit të terapisë me antikoagulantë oralë ose kur UFH jepet në doza të nevojshme për të mbajtur një kateter venoz qendror ose arterial të hapur. Shtatëzënia dhe ushqyerja me gji.
Paralajmërime dhe përkujdesje të veçanta për përdorimin. Edoksaban 15 mg nuk indikohet si monoterapi, pasi mund të shoqërohet me një efikasitet të ulur. Edoksaban 15 mg indikohet vetëm në procesin e kalimit nga Edoksaban 30 mg (pacienti me një ose më shumë faktorë klinikë 2 për ekspozim të shtuar; shih tabelën 1) në VKA, së bashku me një dozë të përshtatshme të VKA.
Rreziku hemorragjik Edoksaban rrit rrezikun e gjakderdhjes dhe mund të shkaktojë gjakderdhje serioze, potencialisht fatale. Roteas, ashtu si antikoagulantët e tjerë, këshillohet të përdoren me kujdes tek pacientët me rrezik të rritur për gjakderdhje. Në rast se shfaqet hemorragji e formës së rëndë administrimi i Roteas duhet të ndërpritet. Në studimet klinike, gjatë trajtimit afatgjatë me edoksaban janë vërejtur më shpesh, në krahasim me trajtimin me VKA, gjakderdhje mukozale (p.sh. epistaksis, hemorragji gastrointestinale, hemorragji urogjenitale) dhe anemi. Për këtë arsye, përveç një mbikëqyrje klinike të kujdesshme, testim laboratorik i hemoglobinës / hematokritit, në rast se gjykohet i përshtatshëm, mund të jetë i dobishëm për të zbuluar ndonjë gjakderdhje okulte. Disa nëngrupe pacientësh, siç detajohen më poshtë, janë në rrezik të rritur për gjakderdhje. Këta pacientë pas fillimit të trajtimit duhet të monitorohen me kujdes për shenjat dhe simptomat e ndërlikimeve të gjakderdhjes dhe anemisë. Çdo rënie e pashpjegueshme e niveleve të hemoglobinës ose presionit të gjakut duhet të bëhet shkak për kërkimin e vendit të një gjakderdhje të mundshme. Efekti antikoagulant i edoksaban nuk mund të monitorohet në mënyrë të besueshme përmes testeve standarde laboratorike. Nuk disponohet ndonjë agjent specifik (antidot) kundër veprimit antikoagulant për edoksaban. Hemodializa nuk kontribuon në mënyrë të konsiderueshme në largimin nga trupi të edoksaban. Të moshuarit
Administrimi i njëkohshëm i edoksaban dhe acidit acetilsalicilik (ASA) në pacientët e moshuar duhet të përdoret me kujdes për shkak të një rreziku potencialisht më të lartë për gjakderdhje.
Dëmtimi i veshikave Sipërfaqja nën kurbë (AUC) plazmatike në subjektet me dëmtime të formës së lehtë (CrCl> 50 - 80 mL/min), të mesme (CrCl 30 - 50 mL/min) dhe të rëndë (CrCl <30 mL/min, por që nuk janë në dializë) rritet përkatësisht me 32%, 74%, dhe 72%, në krahasim me subjektet me funksion normal të veshikave. Në pacientët me sëmundje renale të fazës përfundimtare me të dializës, përdorimi i Roteas nuk është i këshillueshëm. Funksioni i veshikave në NVAF Për edoksaban, në krahasim me warfarinën të dhënë në mënyrë optimale, është vërejtur një pirje dreq zvogëlimit të efikasitetit me rritjen e CrCl për studimin ENGAGE AF-TIMI 48 dhe të dhënës nga studimet E314 dhe ETNA-AF). Në pacientët me NVAF dhe të lartë edoksaban duhet të përdoret vetëm pas një vlerësimi të kujdesshëm të rrezikut individual për tromboemboli dhe gjakderdhje. Vlerësimi i funksionit të veshikave: në të gjithë pacientët në fillim të trajtimit duhet të monitorohet CrCl dhe më pas në rastet ku është e indikuar klinikisht. Dëmtimi i mëlçisë Edoksaban nuk është i këshillueshëm në pacientët me dëmtim të rëndë hepatik. Edoksaban duhet të përdoren me kujdes në pacientët me dëmtime të formës së lehtë ose të mesme të mëlçisë. Pacientët me nivele të rritura të enzimave të mëlçisë (ALT/AST > 2 x ULN) ose me bilirubinë totale ≥ 1.5 x ULN nuk janë përfshirë në studimet klinike. Prandaj, në këtë popullatë edoksaban duhet të përdoret me kujdes. Para fillimit të edoksaban, duhet të bëhet testimi i funksionit të mëlçisë. Në pacientët në trajtim me edoksaban për më shumë se 1 vit kërkëllohet monitorimi periodik i funksionit të mëlçisë. Ndërprerja për shkak të ndërhyrjes kirurgjikale/ndërhyrjes në tjera Në rast se trajtimi antikoagulant duhet të ndërpritet për të zvogëluar rrezikun e gjakderdhjes gjatë procedurave kirurgjikale apo të tjera, edoksaban duhet të ndërpritet sa më shpejt që të jetë e mundur dhe mundësisht të paktën 24 orë para procedurës. Në marrjen e një vendimi nëse procedura duhet të vonohet deri në 24 orë pas dozës së fundit të edoksaban, duhet të vlerësohet rreziku i rritur për gjakderdhje përkundër urgjencës së ndërhyrjes. Edoksaban duhet të rifillohet pas procedurave kirurgjikale ose të tjera menjëherë sapo të jetë arritur hemostaza adekuate, duke mbajtur në konsideratë faktin që koha e fillimit të efektit terapeutik antikoagulant i edoksaban është 1-2 orë. Në rast se gjatë ose pas ndërhyrjes kirurgjikale nuk mund të merren produkte mjekësore nga goja, duhet të merret në konsideratë përdorimi i një antikoagulanti parenteral dhe më pas kalimi në edoksaban një herë në ditë. Ndërprerini me produkte të tjera mjekësore pa ndikoni në hemostazë. Përdorimi i njëkohshëm i barnave të tjera që ndikojnë në hemostazë mund të rrisë rrezikun e gjakderdhjes. Këto përfshijnë acidin acetilsalicilik (ASA), frenuesit e P2Y 12 trombocitarë, agjentë të tjerë antitrombotikë, terapinë fibrinolitike, frenuesit selektiv të rikapjes së serotoninës (SSRI) ose frenuesit e rikapjes së serotoninës dhe noradrenalinës (SNRI), dhe barnat anti-inflamatore jo-steroidë (AJS) kur përdoren në mënyrë kronike. Valvulat protetike të zemrës dhe stenoza mitrale e formës së moderuar deri të rëndë Edoksaban nuk është studiuar në pacientët me proteza valvulare mekanike të zemrës, në pacientët gjatë 3 muajve të parë pas implantimit të një bioprotezë valvulare të zemrës, me ose pa fibrilacion atrial, ose në pacientët me stenozë mitrale të formës së mesme deri të rëndë. Prandaj, përdorimi i edoksaban në këta pacientë nuk është i këshillueshëm. Pacientët me emboli pulmonare hemodinamikisht të paqëndrueshme Në pacientët që kërkojnë trombolizë ose embolektomi pulmonare Edoksaban nuk është e këshillueshme si një alternativë e heparinës së parafraksionuar në pacientët me emboli pulmonare të cilët janë hemodinamikisht të paqëndrueshëm ose që mund të marrin trajtim trombolitik ose që mund ti nënshtrohen embolektomisë pulmonare pasi siguria dhe efikasiteti i edoksaban në këto situata klinike nuk është përcaktuar. Pacientët me kancer aktiv Efikasiteti dhe siguria e edoksaban në trajtimin dhe/ose parandalimin e trombozës së venave të thella në pacientët me kancer aktiv nuk janë përcaktuar. Pacientët me sindromën e mbifosfolipidës. Antikoagulantët oralë me veprim të drejtpërdrejtë (DOAC) përfshirë edoksaban nuk këshillohen për pacientët me historì të trombozës të cilët diagnostikohen me sindromën antifosfolipide. Veçanërisht për pacientët që janë trefish pozitivë (për antitrupat antikoagulant në lupus, antitrupat antikardiolipinë dhe antitrupat anti-beta 2-glikoproteinë I), trajtimi me DOAC mund të shoqërohet me rritje të rëndë të rrezikut të trombozës të përsëritura krahasuar me terapinë me antagonistë të vitaminës K.
Parametrat laboratorik të koagulimit Megjithëse trajtimi me edoksaban nuk kërkon monitorim rutinë, efekti në antikoagulim mund të vlerësohet nga një analizë sasiore e kalibruar e anti-Faktor Xa (FXa) e cila mund të ndihmojë në marrjen e vendimeve klinike në situata të veçanta si, p.sh. mbidozimi dhe kirurgjia urgjente. Edoksaban zgjat testet standarde të koagulimit të tilla si koha e protrombinës (PT), INR, dhe koha e pjesshme e tromboplastinës së aktivizuar (aPTT) si rezultat i frenimit të Faktorit Xa (FXa). Ndryshimet e vërejtura në këto teste të koagulimit kur merret doza terapeutike megjithatë janë të vogla, kanë një shkallë të lartë ndryshueshmërie (variabilitet), dhe nuk janë të dobishme për monitorimin e efektit antikoagulues të edoksaban.
Efektet e padëshiruara Përmbledhje e profilit të sigurisë Profili i sigurisë i edoksaban është vlerësuar në dy studime të Fazës 3 (21,105 pacientë me NVAF dhe 8,292 pacientë me VTE (DVT dhe PE)) dhe nga përvoja e përfituar pas hedhjes në treg. Efektet e padëshiruara të raportuara më të zakonshme të shoqëruara me trajtimin me edoksaban janë epistaksis (7.7%), hematuria (6.9%) dhe anemia (5.3%). Gjakderdhja mund të ndodhë në çdo vend dhe mund të jetë e rëndë dhe madje fatale.

DATA E RISHIKIMIT TË TEKSTIT
10/2023

Zyra Përfaqësuese e Berlin-Chemie AG Rruga e Kavajës, Pallati 3/9/2 Tirana, Albania / Telefoni +355 42 25 99 08

Ky material i referohet barnave me përshkrim dhe i drejtohet vetëm profesionistëve të mjekësisë. RX STATUS

1. Roteas® Summary of Product Characteristics. 10/2023. 2. Giugliano RP et al. N Engl J Med. 2013;369:2093–2104. 3. Kirchhof P et al. Eur Heart J. 2023;44(Suppl 2):ehad655.552.

AL-ROT-02-2026_MFLOW - 07/2026

REDUKTIM SUPERIOR I PRESIONIT TË GJAKUT [1*]

NË PACIENTËT ME HIPERTENSION ARTERIAL [2]



AMLO/OLME/HCTZ: kombinim fuqishëm në pacientët me kontroll të pamjaftueshëm të presionit të gjakut në terapinë e dyfishtë të kombinuar. [1]

Ulje superiore e presionit të gjakut krahasuar me terapinë e dyfishtë të kombinuar. [3]

Opsion efektiv për hipertensionin rezistent ndaj trajtimit. [4]

Përputhshmëri më e lartë me kombinim në një tabletë kundrejt kombinimit të barnave në tableta të ndryshme. [5]

KALISTRA PLUS



PËRMBLEDHJE E KARAKTERISTIKAVE TË PRODUKTIT

Kalistra Plus 20 mg/5 mg/12,5 mg tableta të veshura me film Kalistra Plus 40 mg/5 mg/12,5 mg tableta të veshura me film Kalistra Plus 40 mg/5 mg/25 mg tableta të veshura me film Kalistra Plus 40 mg/10 mg/25 mg tableta të veshura me film PËRBËRJA SASIORE DHE CILËSORE Kalistra Plus tableta të veshura me film FORMA FARMACEUTIKE Tabletë e veshur me film. Kalistra Plus 20 mg/5 mg/12,5 mg tableta të veshura me film. Tabletë e veshur me film, me ngjyrë portokalli të hapur, me formë të rrumbullakët me diametër 8 mm, në njërën anë të së cilës është gdhendur C51. Kalistra Plus 40 mg/5 mg/12,5 mg tableta të veshura me film. Tabletë e veshur me film, me ngjyrë të verdhë të lehtë, me formë të rrumbullakët me diametër 9,5 mm, në njërën anë të së cilës është gdhendur C53. Kalistra Plus 40 mg/5 mg/25 mg tableta të veshura me film. Tabletë e veshur me film, me ngjyrë të verdhë të lehtë, me formë ovale me përmasa 15 x 7 mm, në njërën anë të së cilës është gdhendur C54. Kalistra Plus 40 mg/10 mg/25 mg tableta të veshura me film. Tabletë e veshur me film, me ngjyrë të kuqe në gri, me formë ovale me përmasa 15 x 7 mm, në njërën anë të së cilës është gdhendur C57. VEÇORITË KLINIKE Indikimet terapeutike Trajtimi i hipertensionit esencial. Terapia shtesë Kalistra Plus indikohet në pacientë të rritur presioni i gjakut të cilëve nuk kontrollohet në mënyrë të përshtatshme nga kombinimi i olmesartan medoksomilit dhe amlodipinës, i marrë në trajtim e një formulimi që përmban të dy komponentët (kombinim fikс-dysh). Terapia zëvendësuese Kalistra Plus indikohet si terapi zëvendësuese në pacientë të *rritur* presioni i gjakut të të cilëve kontrollohet në mënyrë të përshtatshme nga kombinimi i olmesartan medoksomilit, amlodipinës dhe hidroklortiazidit, marrë në trajtim e një formulimi që përmban dy komponentë (olmesartan medoksomil dhe amlodipinë ose olmesartan medoksomil dhe hidroklortiazid) dhe një formulimi që përmban një komponent (hidroklortiazid ose amlodipinë). Doza e këshilluar e Kalistra Plus është 1 tabletë në ditë. Kalistra Plus 20 mg/5 mg/12,5 mg mund të përdoret në pacientë presioni i gjakut të cilëve nuk kontrollohet në mënyrë të përshtatshme nga kombinimi i olmesartan medoksomil 20 mg dhe amlodipinë 5 mg të marrë në trajtim e një formulimi që i përmban të dy komponentët ose në pacientë presioni i gjakut të cilëve nuk kontrollohet në mënyrë të përshtatshme nga Kalistra Plus 40 mg/5 mg/12,5 mg. Kalistra Plus 40 mg/5 mg/25 mg mund të përdoret në pacientë presioni i gjakut të cilëve nuk kontrollohet në mënyrë të përshtatshme nga Kalistra Plus 40 mg/5 mg/12,5 mg. Kalistra Plus 40 mg/10 mg/25 mg mund të përdoret në pacientë presioni i gjakut të cilëve nuk kontrollohet në mënyrë të përshtatshme nga Kalistra Plus 40 mg/5 mg/25 mg ose nga Kalistra Plus 40 mg/5 mg/25 mg. Terapia zëvendësuese Pacientët në të cilët mbahen në kontroll nga përdorimi i dozave të stabilizuara të olmesartan medoksomilit, amlodipinës dhe hidroklortiazidit të marra në të njëjtën kohë si formulim që përmban dy komponentë (olmesartan medoksomil dhe amlodipinë ose olmesartan medoksomil dhe hidroklortiazid) dhe formulim që përmban një komponent (hidroklortiazid ose amlodipinë) mund të kalojnë në trajtim me Kalistra Plus që përmban të njëjtat doza të secilit komponent.Doza maksimale e këshilluar e Kalistra Plus është 40 mg/10 mg/25 mg në ditë. Të mosthuajti (me moshë 65 vjec ose më shumë). Në pacientët e mosthuar këshillohet kujdes, përfshi edhe kontrollin më të shpeshtë të presionit të gjakut, veçanërisht kur përdoren dozat maksimale të Kalistra Plus 40 mg/10 mg/25 mg në ditë. Ritja e dozave tek të mosthuarit duhet të bëhet me kujdes. Të dhënat lidhur me përdorimin e Kalistra Plus në pacientët me moshë 75 vjec ose më shumë janë mjaft të kufizuara. Për këtë arsye, këshillohet shumë kujdes, përfshi edhe kontrollin më të shpeshtë të presionit të gjakut. Përdorimi i Kalistra Plus në pacientët me dëmtim të formës së rëndë të funksionit të veshkave (klireni i kreatininës < 30 mL/min) është i kundërindikuar. Dëmtimi i funksionit renal Në pacientët me dëmtim të formës së lehtë deri të mesme të funksionit të veshkave (klireni i kreatininës 30 – 60 mL/min), për shkak të përvejës së kufizuar me dozat 40 mg olmesartan medoksomil në këta pacientë, doza maksimale shtesë Kalistra Plus 20 mg/5 mg/12,5 mg. Në pacientët me dëmtim të formës së mesme të funksionit të veshkave këshillohet që të monitorohen përqendrimet e kalimit dhe kreatininës në serum. Përdorimi i Kalistra Plus në pacientët me dëmtim të formës së rëndë të funksionit të veshkave (klireni i kreatininës < 30 mL/min) është i kundërindikuar. Dëmtimi i funksionit hepatik Kalistra Plus duhet të përdoret me kujdes në pacientët me dëmtim të formës së lehtë të funksionit të mëlçisë. Në pacientët me dëmtim të formës së mesme të funksionit të mëlçisë doza maksimale nuk duhet të kalojë Kalistra Plus 20 mg/5 mg/12,5 mg një herë në ditë. Në pacientët me dëmtim të funksionit të mëlçisë këshillohet një kontroll nga afër i presionit të gjakut dhe i funksionit të veshkave. Ashtu si në rastin e barnave të tjerë antagonistë të kalcitumit, në pacientët me dëmtim të funksionit të mëlçisë gjysmëjeta e amlodipinës zgjatet dhe për këtë arsye nuk mund të jepen këshilla të përcaktuara lidhur me dozimin. Në këta pacientë Kalistra Plus duhet të përdoret me kujdes. Farmakokinetika e amlodipinës nuk është studiuar në pacientët me dëmtim të formës së rëndë të funksionit të mëlçisë. Në pacientët me dëmtim të funksionit të mëlçisë amlodipina duhet të fillohet me doza të ulëta dhe titrimi i dozës duhet të bëhet me ngadalë. Përdorimi i Kalistra Plus në pacientët me dëmtim të formës së rëndë të funksionit të mëlçisë, kolestazë ose obstruksion të rrugëve biliare është i kundërindikuar. Papullata pediatrike Kalistra Plus nuk këshillohet të përdoret në pacientët me moshë nën 18 vjec për shkak të mungesës së të dhënave mbi sigurinë dhe efikasitetin. Mënyra e përdorimit: Tableta duhet të gëlltitet e shoqëruar me ujë sasi të mjaftueshme lëngu (p.sh. një gotë me ujë). Tableta nuk duhet të përtypet dhe duhet të merret në njëjtën kohë të ditës. Kalistra Plus mund të merret njëkohësisht me ushqimin ose pavarësisht prej tij. Kundërindikimet Mbindjeshmëria ndaj lëndëve vepruese, derivateve të dihidropiridinave ose lëndëve që rijedhin nga sulfonamidi (megenëse hidroklortiazidi është një bar që rijedh nga sulfonamidi) ose ndaj ndonjë prej lëndëve të tjera përbërëse (ekscipientëve) të produktit. Dëmtimi i formës së rëndë i funksionit të veshkave. Hipokalaemia, hiperkalcemia, hiponatremia. Dëmtimi i formës së rëndë i funksionit të mëlçisë, kolestaza dhe cirrogulimet obstruktive të rrugëve biliare. Tremestri i 2-të dhe i 3-të i shtatzënisë. Përdorimi i njëkohshëm i Kalistra Plus me produkte mjekësore që përmbajnë aliskiren dëmtoi i kundërindikuar në pacientët që vuajnë nga diabeti mellit ose nga dëmtimi i funksionit të veshkave (Ritmi i Filtrimit Glomerular < 60 mL/min/1,73 m2). Për shkak se përmban amlodipinë, Kalistra Plus është e kundërindikuar në pacientët me: shok (përfshi shokun kardiogjen), hipotension të theksuar, obstruksion të traktit të hedhjes të ventrikulit të majtë (p.sh. stenozë e aortës e shkalles së lartë), insuficiencë kardiake të paqëndrueshme nga pikëpamja hemodinamike, pas infarktit akut të miokardit. Paralajmërime dhe përkujdesje të veçanta gjatë përdorimit Pacientët me hipovolemi ose pakësim të natrium: Në pacientët të cilët kanë pakësim të vëllimit qarkullues dhe/ose të natrium: për shkak të trajtimit të fuqishëm me diuretikë, dietës së kufizuar me kripë, ngа diarreja ose të vjellat, sidomos pas marrjes së dozës së parë, mund të shfaqet hipotension simptomatik. Këto gjendje duhet të korrigjohen përpara se të fillohet trajtimi me Kalistra Plus, ndërkohë që këshillohet mbikëqyrje e ngushtë mjekësore në fillim të trajtimit. Gjendje të tjera të shoqëruara me rritje të sistemit renino-angiotenzinë-aldosteron: Në pacientët në të cilët tonusi vaskular dhe funksioni i veshkave varet kryesisht nga veprimtaria e sistemit renino-angiotenzinë-aldosteron (p.sh. pacientët me insuficiencë kardiake kongjestive të formës së rëndë ose sëmundje shoqëruese të veshkave, përfshirë stenozën e arteries renale), trajtimi me produkte mjekësore që ndikojnë në këtë sistem mund të shoqërohet me hipotension akut, azotemi, oliguri ose, rrallë, me insuficiencë renale akute. Hipertensioni renovaskular: Ka një rritje të rrezikut për shfaqje të hipotensionit të formës së rëndë dhe insuficiencës renale kur pacientët me stenozë të të dy arteriove renale ose stenozë të arteries renale të të vetmes veshkë funksionale trajtohen me produkte mjekësore që ndikojnë në sistemin renin-angiotenzinë-aldosteron. Dëmtimi i funksionit të veshkave dhe transplanti i veshkave: Kur Kalistra Plus përdoret në pacientë me dëmtim të funksionit të veshkave, këshillohet që nivelet të serum të kalumit dhe kreatininës të kontrollohen periodikisht. Kalistra Plus nuk këshillohet që të përdoret në pacientë me dëmtim të formës së rëndë të funksionit të veshkave (klireni i kreatininës < 30 mL/min). Në pacientë me dëmtim të funksionit të veshkave mund të shfaqet azotemi e lidhur me përdorimin e diuretikëve tiazidikë. Në rast se dëmtimi i funksionit të veshkave është dukshëm përparues (dëmtim progresiv), ateheré është e nevojshme që trajtimi të rivlerësohet me kujdes, duke marrë në konsideratë edhe ndërprerjen e trajtimit me diuretik. Nuk ka përvojë lidhur me përdorimin e Kalistra Plus në pacientë të cilët para pak kohësh i janë rënshtuar transplanti të veshkave ose që vuajnë sëmundje e veshkave në stadin përfundimtar (klireni i kreatininës < 12 ml/min). Bllokimi i dyfishtë i sistemit reninë-angiotenzinë-aldosteron (SRAA): Ka të dhëna që përdorimi i njëkohshëm i frenuesve të ACE, bllokuesve të receptorëve të angiotenzinës II ose aliskirenit, rrit rrezikun e hipotensionit, hiperkalemisë dhe dëmton (pakëson) funksionin e veshkave (përfshirë insuficiencën renale akute). Për këtë arsye, bllokimi i dyfishtë i SRAA përmes përdorimit të kombinuar të frenuesve të ACE, bllokuesve të receptorëve të angiotenzinës II ose aliskirenit nuk është i këshillueshëm. Në rastet kur terapia përmes bllokimit të dyfishtë konsiderohet absolutisht e nevojshme, kjo duhet të jepet vetëm nën mbikëqyrje të specializuar dhe funksioni renal, elektroliteti dhe presioni i gjakut duhet të monitorohen nga afër dhe më mënyrë të shpeshtë. Në pacientët me nefropati diabetike, frenuesit e ACE dhe bllokuesit e receptorit të angiotenzinës II nuk duhet të përdoren njëkohësisht. Dëmtimi i funksionit të mëlçisë: Në pacientët me dëmtim të funksionit të mëlçisë ekspozimi sistemik ndaj amlodipinës dhe olmesartan medoksomilit është i rritur. Për më tepër, në pacientët me dëmtim të funksionit të mëlçisë ose sëmundje progresive të mëlçisë, ndryshime qoftë edhe të vogla në balancën e lëngjeve dhe elektroliteve për shkak të trajtimit me tiazidikë mund të precipitojnë komën hepatike. Kur Kalistra Plus duhet të përdoret në pacientë me dëmtim të lehtë deri mesatar të funksionit të mëlçisë, kolestazë dhe sëmundje të tjera të mëlçisë, doza e olmesartan medoksomilit nuk duhet të kalojë 20 mg. Në pacientët me dëmtim të funksionit të mëlçisë, amlodipina duhet të fillohet me dozën më të vogël dhe gjithashtu kështillohet të tregohet kujdes si në fillim të trajtimit, ashtu edhe më tej doza. Kalistra Plus është e kundërindikuar në pacientët me dëmtim të formës së rëndë të funksionit të mëlçisë, kolestazë dhe obstruksion të rrugëve biliare. Stenoza e valvulës aortike dhe mitrale, kardiomiopatia hipertrofike obstruktive. Aldosteronizmi parësor: Pacientët me aldosteronizëm parësor në përgjithësi nuk i përgjigjen trajtimit me barna antihipertensive që veprojnë duke frenuar sistemin reninë-angiotenzinë-aldosteron. Për këtë arsye, përdorimi i Kalistra Plus në këta pacientë nuk është i këshillueshëm. Efektet metabolike dhe endokrine: Trajtimi me tiazidikë mund të dëmtojë tolerancën ndaj glukozës. Në pacientët diabetikë mund të jetë e nevojshme që të përshtaten dozat e insulinës ose barnave antidiabetikë që merren nga goja. Gjatë trajtimit me tiazidikë diabeti mellit latent mund të shfaqet klinikisht. Trajtimi me diuretikë tiazidikë gjithashtu dihet se mund të shoqërohet me shfaqjen e efektave të padëshirueara të tilla si rritja e niveleve të kolesterolit dhe triglicerideve. Gjatë trajtimit me tiazidikë mund të shfaqet hiperuricemi ose, në disa pacientë, mund të precipitojnë krizat e podagrës (gutës). Çregullimet e balancës së elektroliteve: Ashtu si për çdo pacient që trajtohet me diuretikë, është e nevojshme që në mënyrë periodike, në intervale të përshtatshme kohore, të kontrollohen përqendrimet e elektroliteve në serum. Tiazidikët, përfshi hidroklortiazidin, mund të shkaktojnë çregullim të balancës se lëngjeve dhe elektroliteve (përfshi hipokaleminë, hiponatreminë dhe alkalozën hipokloremike). Shenja paralajmëruese të prishjes së balancës së lëngjeve dhe elektroliteve janë tharja e gojës, etja, dobësia, letargjia, përgjumja, nervozizmi, dhimbjet ose krampet muskulore, lodhja e muskujve, hipotensioni, oliguria, takikardia, dhe çregullimet gastrointestinale të tilla si të përzierat dhe të vjellat. Ëreciku i hipokalemisë është më i mundi në pacientët me cirrozë të mëlçisë, në pacientët që përjetojnë diurezë të shpejtë, në pacientët që nuk marrin nga goja sasitë e nevojshme të elektroliteve dhe në pacientët që njëkohësisht trajtohen me kortikosteroidë ose ACTH. Nga ana tjetër, për shkak të antagonizmit të receptorëve të angiotenzinës II- (ATT) pra përbërësit olmesartan medoksomil që përmban Kalistra Plus mund të shfaqet hiperkalemia, sidomos në rrani të dëmtimit të funksionit të veshkave dhe/ose insuficiencës kardiake, dhe diabetit mellit. Në pacientët e rrezikuar këshillohet që nivelet e kalumit në serum të kontrollohen në mënyrë të kujdeshme. Diuretikët kursyes të kalumit, shtojcat që përmbajnë kalium ose zëvendësuesit e kripës që përmbajnë kalium, si edhe produktet e tjera mjekësore që mund të rrisin nivelet e kalumit në serum (p.sh. heparina) kur është e nevojshme që të përdoren njëkohësisht me Kalistra Plus duhet të administrohen me kujdes, ndërkohë që nivelet e kalumit në serum të kontrollohen në mënyrë të shpeshtë . Nuk ka të dhëna që olmesartan medoksomil zvogëlon ose parandalon hiponatreminë që nxit diuretiku. Deficiti i klorit në përgjithësi është i formës së lehtë dhe zakonisht nuk kërkon trajtim. Tiazidikët mund të pakësojnë jastëkëtjen në urinë të kalcitumit dhe, për pasojë, mund të shkaktojnë një shtim intermitent, të formës së lehtë, të kalcitumit në serum, në mungesë të çregullimeve të njohura të metabolizmit të kalcitumit. Hiperkalcemia mund të jetë shenjë e hiperparatiroidizmit të fshehur. Tiazidikët duhet të ndërpritën para kryerjes së testeve të funksionit të paratiroides. Tiazidikët mund të shtojnë jashtëqitjen në urinë të magnezit, veprim ky që mund të shkaktojë hipomagnezemi. Në kushtet e mottit të rxehtë në pacientët edematozë mund të shfaqet hiponatremi pa hollimi. Litiumi: Ashtu si në rastin e antagonistëve të tjerë të receptorëve të angiotenzinës II, përdorimi i njëkohshëm i Kalistra Plus dhe litiumit nuk ështeë i këshillueshëm. Insuficienca kardiake: Si pasojë e frenimit të sistemit reninë-angiotenzinë-aldosteron, është e pritshme që në pacientët e prirur të shfaqen ndryshime të funksionit renal. Në pacientët me insuficiencë kardiake të formës së rëndë, funksioni renal i të cilëve mund të varet kryesisht nga veprimtaria e sistemit reninë-angiotenzinë-aldosteron, trajtimi me barna frenues të enzimës konvertuese të angiotenzinës (ACE inhibitorë) dhe antagonistë të receptorëve të angiotenzinës është shoqëruar me oliguri dhe/ose azotemi progresive dhe (rrallë) me insuficiencë renale akute dhe/ose vdekje. Pacientët me insuficiencë kardiake duhet të trajtohen me kujdes. Në një studim afatgjatë, të kontrolluar përkundrejt placebos, ku amlodipina u përdor në pacientë me insuficiencë kardiake të formës së rëndë (NYHA III dhe IV), incidence e raportuar e edemës pulmonare ishte më e lartë në grupin e trajtuar me amlodipinë krahasuar me grupin që mori placebo. Bllokuesit e kanalevе të kalcitumit, përfshi dhe amlodipinën, duhet të përdoren me kujdes në pacientët me insuficiencë kardiake kongjestive pasi mund të shtojnë rreziкun për ngjarje të ardhshme kardiovaskulare dhe vdekshmërinë. Enteropatia e ngjashme me sëmundjen celiake (sprunë). Në raste shumë të rralla, në pacientët që marrin olmesartan, disa muaj deri në vite pas fillimit të barit, janë raportuar raste me diarre kronike, të formës së rëndë, me humbje të konsiderueshme peshe, ndoshta të shkaktuara nga një reaksion mbindjeshmërie i vonuar i ekaluar. Biopsitë e zorrëve të pacientëve shpesh demonstrojnë atrofi të vilevе. Në raste pacientë zhvillon këto simptoma gjatë trajtimit me olmesartan dhe në mungesë të ndonjë shkaku tjetër të dukshëm, trajtim me olmesartan medoksomil nuk duhet të rifillohet. Nëse diarrea nuk përmirësohet gjatë javës pas ndërprerjes, duhet të merren parasysh këshilla të tjera të specializuara (p.sh. një gastroenterologi). Efuzioni koroidal, miopia akute dhe glaukoma sekondare me kënd të mbyllur: Hidroklortiazidi, një sulfonamid, mund të shkaktojë një reaksion idiosinkratik, duke rezultuar në efuzion koroidal me defekte të fushës vizive, miopi akute të përkohshme dhe glaukomë akute me kënd të mbyllur. Simptomat përfshijnë fillimin akut të zvogëlimit të mprehtësisë së shikimit ose dhimbjen e syrit dhe zakonisht ndodhin brenda disa orëve e deri në javë pas fillimit të përdorimit të barit. Glaukoma akute me kënd të mbyllur e patrajtuar mund të çojë në humbje të përhershme të shikimit. Trajtimi fillestar është të ndërpreріa e hidroklortiazidit sa më shpejt të jetë e mundur. Trajtimet e shpejta mjekësore ose kirurgjikе mund të duhet të merren parasysh nëse presioni intraokular mbetet i pakontrolluar. Faktorët e rrezikut për zhvillimin e glaukomës akute me kënd të mbyllur mund të përfshijnë një histori të alergjisë ndaj sulfonamideve ose penicilinës. Shtatzënia: Antagonistët e receptorëve të angiotenzinës II nuk duhet të fillohen gjatë shtatzënisë. Për sa kohë që vazhdimi i trajtimit me antagonistët të angiotenzinës II konsiderohet i domosdoshëm, pacientet të cilat planifikojnë të mbetën shtatzëna duhet të kalohen në regjime terapeutike me barna të tjerë antihipertensivë, të cilëve i njihet profili i sigurisë në kushtet e përdorimit gjatë shtatzënisë. Menjëherë, sapo diagnostikohet një shtatzëni, trajtimi me antagonistët të receptorëve të angiotenzinës II duhet të ndërpritet dhe, në rast se konsiderohet e përshtatshme, duhet të filohet një trajtim alternativ .Popullata pediatrike: Kalistra Plus nuk është e indikuar në fëmijë dhe të ri) me moshë nën 18 vjec. Të mosthuarit: Në të mosthuarit, rritja e dozës duhet të bëhet me kujdes. Mbindjeshmëria ndaj dritës: Janë raportuar raste të mbindjeshmërisë ndaj dritës (reaksione fotosensitiviteti) gjatë përdorimit të diuretikëve tiazidikë. Në rast se gjatë trajtimit me Kalistra Plus vërehen reaksione të mbindjeshmërisë ndaj dritës, këshillohet që trajtimi të ndërpritet. Në rast se rifillimi i trajtimit me diuretikë konsiderohet i nevojshëm, këshillohet që të mbrohen sipërfaqet e trupit që ekspozohen ndaj dritës së diellit ose dritës artificiale. Kanceri i lëkurës jo-melanocitik Në dy studime epidemiologjike të bazuar në Regjistrin Kombëtar Danez të Kancerit, është vënë re një risk i rritur për kancer të lëkurës jo-melanocitik (NMSC) [carcinoma me qelizа bazale (BCC) dhe karcinoma me qeliza skuamoze (SCC)] në rastet e ekspozimit me doza rritëse kumulative të hidroklortiazidit. Veprimet fotosensitive të HCTZ mund të veprojnë si një mekanizëm i mundshëm për NMSC.Pacientët që marrin HCTZ duhet të informohen për rrisкun e NMSC dhe të këshillohen rregullisht që të kontrollojnë lëkurën e tyre për ndonjë lezion të ri dhe të raportojnë menjëherë çdo lezion lëkure të dyshimtë. Përdorimi duhet të këshillohen për masa parandaluese të mundshme si p.sh.: ekspozimi i kufizuar ndaj rrezeve të diellit dhe atyre UV dhe në rast ekspozimi, mbrojtje e përshtatshme me qëllimin për të minimizuar rrisкun e kancerit të lëkurës. Lezione të dyshuara në lëkurë duhet të kontrollohen menjëherë, duke përfshirë mundësinë edhe ekzaminimin histologjik të biopsive. Përdorimi i HCTZ mund të ketë nevojë të rikonsiderohet në pacientët të cilët kanë pasur më parë NMSC. Toksicitetі akut respirator Pas marrjes së hidroklortiazidit, janë raportuar raste shumë të rralla të rënda të toksicitetit akut respirator, përfshirë sindromën e distresit akut respirator (ARDS). Edema pulmonare zakonisht zhvillohet brenda disa minutave deri në disa orë pas marrjes së hidroklortiazidit. Në fillim, simptomat përfshijnë dispne, ethe, përkeqësim pulmonar dhe hipotension. Nëse dyshohet për diagnozën e ARDS, Kalistra® Plus duhet të tërhiqet dhe të jepet trajtimi i duhur. Hidroklortiazidi nuk duhet t'u administrohet pacientëve që kanë pësuar më parë ARDS pas marrjes së hidroklortiazidit. Të tjera: Ashtu si me çdo bar tjetër antihipertensiv, një ulje e theksuar e presionit të gjakut në pacientët me sëmundje iskemike të zemrës ose me sëmundje iskemike cerebrovaskulare mund të shkaktojë një infarkt miokardi ose një insult cerebral. Reaksionet e mbindjeshmërisë ndaj hidroklortiazidit mund të shfaqen si në pacientët alergjikë ose që vuajnë nga astma bronkiale, ashtu edhe në pacientët pa këto probleme, por ato janë më të mundshme në rastin e parë. Në pacientët që përdorin diuretikë tiazidikë ka pasur raportime të rrallа/zëmtë ose të ekzistuimit të lupusit eritematoz sistemik. Ashtu si në rastin e barnave të tjerë antagonistë të angiotenzinës II, efektі i olmesartan medoksomilit në ujën e presionit të gjakut është më pak i shprehur në pacientët zezakë krahasuar me pacientët jo zezakë, megjithëse ky efekt nuk është vërejtur në një nga tre studimet klinike të kryera me Kalistra Plus, në të cilin ishin të përfshirë pacientë zezakë (30%). Ky bar përmban më pak se 1 mmol natrium (23mg) për çdo tabletë të veshur me film, që do të thotë se është praktikisht pa natrium.

DATA E RISHIKIMIT TË TEKSTIT 05/2023

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Ky material i referohet barnave me përshkrim dhe i drejtohet vetëm profesionistëve të mjekësisë. RX STATUS

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TABLE OF CONTENTS

HLA CLASS I AND II ALLELE DISTRIBUTION IN ALBANIAN PATIENTS WITH AUTOIMMUNE THYROID DISEASE 8

Dorina Ylli, Megi Lekbello, Marjeta Kermaj,Violeta Hoxha, Erkena Shyti, Donika Kasemi, Zamira Ylli, Genc Sulcebe 8

CLINICO-PATHOLOGICAL CHARACTERISTICS OF GASTRIC CANCER PATIENTS 17

Bledi Kreka, Martiola Kola, Dea Kreka,Drini Shehi, Arvit Llazani, Ervin Toci, Manika Kreka,Arvin Dibra 17

FACTORS INFLUENCING HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH DIABETIC NEPHROPATHY: A CROSS-SECTIONAL STUDY 26

Nevi Pasko, Teuta Dedej, Elvana Rista, Ariana Strakosha, Alba Xhoku, Vilma Cadri, Amantia Imeraj 26

OTOACUSTIC EMISSION MEASUREMENTS IN COMPARISON TO AUDIOMETRY FOR THE FOLLOW-UP OF HEARING IN HEMODIALYSED PATIENTS 36

Evis Bendo, Nirian Bendo 36

IMMUNOGENETIC FACTORS IN AUTOIMMUNE THYROID DISEASES: CENTRAL ROLE OF HLA IN DISEASE SUSCEPTIBILITY 43

Megi Lekbello, Dorina Ylli, Marjeta Këmaj, Violeta Hoxha, Klodiana Poshi 43

PHYSIOPATHOLOGICAL MECHANISMS OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE DISEASES 50

Anxhela Qirko (Gurakuqi), Taulant Gishto 50

RECENT DEVELOPMENTS IN HFpEF AND ATRIAL FIBRILLATION 57

Somida Kuka, Eneida Hoxha, Margarita (Gjata) Resuli 57

WHEN TREATMENT BECOMES THE TRIGGER: POLYPHARMACY AS A HIDDEN CAUSE OF ACUTE CLINICAL DETERIORATION IN INTERNAL MEDICINE 65

Eneida Hoxha, Ledio Collaku, Somida Kuka, Pandush Pojani, Xhesika Habilaj, Margarita Gjata 65

INTENSIVE CARE MANAGEMENT OF PATIENTS WITH SCLERODERMA: A CASE SERIES 78

Dorina Ruci, Krisli Serani, Vilson Ruci, Arsel Dizdari, Entela Shkodrani 78

THE ROLE OF VIDEONYSTAGMOGRAPHY AND MAGNETIC RESONANCE IMAGING IN RECURRENT POSITIONAL VERTIGO: A CASE REPORT 85

Evis Bendo, Nirian Bendo 85

OUR EXPERIENCE IN THE DIAGNOSIS AND MANAGEMENT OF PSYCHOCUTANEOUS DISORDERS IN A TERTIARY CARE CENTER IN ALBANIA. 90

Migena Vargu, Sabina Dedej, Eriselda Kurushi, Anxhela Nisi, Samuele Vargu, Petrit Vargu 90

HEPARIN-INDUCED DELAYED-TYPE HYPERSENSITIVITY REACTION: TWO CASE REPORTS AND MANAGEMENT STRATEGIES 101

Mehmet Hoxha, Ester Ndreu 101

NODULAR LESIONS IN AN ELDERLY PATIENT REVEALED BY DERMOSCOPY. 108

Migena Vargu, Sabina Dedej, Eriselda Kurushi, Anxhela Nisi, Samuele Vargu, Petrit Vargu 108

ORIGINAL ARTICLE

HLA CLASS I AND II ALLELE DISTRIBUTION IN ALBANIAN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

Dorina Ylli[1], Megi Lekbello[1], Marjeta Kermaj, Violeta Hoxha[1], Erkena Shyti[2], Donika Kasemi[2], Zamira Ylli[2], Genc Sulcebe[2]

[1]University of Medicine Tirana

[2]Research Center of Biotechnology and Genetics, Tirana, Albania

Corresponding E-mail: dorina.ylli@umed.edu.al

ABSTRACT

Background. Autoimmune thyroid diseases (ATD), including Hashimoto's thyroiditis and Graves' disease, are among the most common autoimmune disorders and arise from complex interactions between genetic susceptibility and environmental factors. The human leukocyte antigen (HLA) region on chromosome 6p21 plays a major role in immune regulation and disease susceptibility. However, the distribution of HLA alleles varies across populations, and data from Balkan populations remain limited. This study aimed to investigate the distribution of HLA class I and class II alleles in Albanian patients with autoimmune thyroid disease.

Methods. This study included 68 patients diagnosed with autoimmune thyroid disease at the Endocrinology Unit of the University Hospital Center "Mother Teresa", Tirana, between 2023 and 2025. The cohort comprised 51 patients with Hashimoto's thyroiditis and 17 with Graves' disease. Genomic DNA was extracted from peripheral blood samples, and allele-level HLA genotyping for class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DRB1, HLA-DQB1) loci was performed using PCR with sequence-specific primers (PCR-SSP). Allele frequencies were calculated by direct gene counting and expressed as percentages with 95% confidence intervals.

Results. The mean age of participants was 42.2 ± 11 years, with a strong female predominance (91%). Among HLA class I alleles, A02:01 was the most frequent allele (38.0%), followed by A01:01 and A24:02 (9.9% each). At the HLA-B locus, B51:01 (16.2%), B18:01 (14.6%), and B35:01 (13.8%) were the most common alleles. For the HLA-C locus, C07:01 was predominant (22.3%), followed by C12:03 (17.4%) and C02:02 (10.7%). Among class II alleles, DRB111:01 showed the highest frequency (26.6%), followed by DRB116:01 (18.8%) and DRB104:01 (12.5%). At the HLA-DQB1 locus, DQB103:01 was the most frequent allele (35.5%), followed by DQB105:02 (19.4%) and DQB102:01 (12.1%). Compared with previously published European data, the Albanian cohort demonstrated a relatively higher frequency of DRB111 and lower frequency of DRB1*03.

Conclusion. This study provides the first characterization of HLA class I and class II allele frequencies in Albanian patients with autoimmune thyroid disease. The predominance of DRB111 and DQB103 suggests a distinctive immunogenetic profile that partially overlaps with other Mediterranean populations. These findings contribute to understanding the population-specific genetic background of autoimmune thyroid disease and highlight the need for larger studies in Balkan populations.

Keywords. Autoimmune thyroid disease, HLA polymorphism, Albanian population

SHPËRNDARJA E ALELEVE HLA TË KLASËS I DHE II TE PACIENTËT SHQIPTARË ME SËMUNDJE AUTOIMUNE TË GJËNDRËS TIROIDE

ABSTRAKT

Hyrja. Sëmundjet autoimune të tiroides (SAT), përfshirë tiroiditin e Hashimotos dhe sëmundjen e Graves, janë ndër çrregullimet autoimune më të shpeshta dhe lindin nga ndërveprimi kompleks midis predispozitës gjenetike dhe faktorëve mjedisorë. Rajoni i antigjenit leukocitar human (HLA) në kromozomin 6p21 luan një rol të rëndësishëm në rregullimin e përgjigjes imune dhe në ndjeshmërinë ndaj sëmundjes. Megjithatë, shpërndarja e aleleve HLA ndryshon ndërmjet popullatave dhe të dhënat për popullatat e Ballkanit janë ende të limituara. Qëllimi i këtij studimi ishte të investigojë shpërndarjen e aleleve të klasës I dhe klasës II të HLA tek pacientët shqiptarë me sëmundje autoimune të tiroides.

Metodat. Studimi përfshiu 68 pacientë të diagnostikuar me sëmundje autoimune të tiroides në Shërbimin e Endokrinologjisë të Qendrës Spitalore Universitare "Nënë Tereza", Tiranë, gjatë periudhës 2023–2025. Grupi përbëhej nga 51 pacientë me tiroidit kronik Hashimoto dhe 17 pacientë me sëmundje të Graves. ADN-ja gjenomike u ekstraktua nga mostrat e gjakut periferik dhe gjenotipizimi i HLA në nivel aleli për lokuset e klasës I (HLA-A, HLA-B, HLA-C) dhe klasës II (HLA-DRB1, HLA-DQB1) u krye duke përdorur metodën PCR me primerë specifikë për sekuencën (PCR-SSP). Frekuencat alelike u llogaritën me metodën e numërimit direkt të gjeneve dhe u shprehën në përqindje me intervale besueshmërie 95%.

Rezultatet. Mosha mesatare e pjesëmarrësve ishte 42.2 ± 11 vjeç, me predominancë të theksuar të femrave (91%). Ndër alelet e klasës I të HLA, A02:01 ishte aleli më i shpeshtë (38.0%), i ndjekur nga A01:01 dhe A24:02 (secila 9.9%). Në lokusin HLA-B, alelet më të shpeshta ishin B51:01 (16.2%), B18:01 (14.6%) dhe B35:01 (13.8%). Për lokusin HLA-C, C07:01 ishte aleli predominues (22.3%), i ndjekur nga C12:03 (17.4%) dhe C02:02 (10.7%). Ndër alelet e klasës II, DRB111:01 kishte frekuencën më të lartë (26.6%), i ndjekur nga DRB116:01 (18.8%) dhe DRB104:01 (12.5%). Në lokusin HLA-DQB1, DQB103:01 ishte aleli më i shpeshtë (35.5%), i ndjekur nga DQB105:02 (19.4%) dhe DQB102:01 (12.1%). Krahasuar me të dhënat e publikuara më parë për popullatat evropiane, kohorta shqiptare tregoi një frekuencë relativisht më të lartë të DRB111 dhe një frekuencë më të ulët të DRB1*03.

Përfundimi. Ky studim paraqet karakterizimin e parë të frekuencave të aleleve të klasës I dhe klasës II të HLA tek pacientët shqiptarë me sëmundje autoimune të tiroides. Predominanca e aleleve DRB1*11 dhe DQB1*03 sugjeron një profil imunogjenetik të veçantë që mbivendoset pjesërisht me popullatat e tjera mesdhetare. Këto rezultate hedhin themele për kuptimin e bazës gjenetike specifike të popullatës për sëmundjet autoimune të tiroides dhe theksojnë nevojën për studime të tjera në popullatat e Ballkanit.

Fjalë kyçe: sëmundjet autoimune të gjëndrës tiroide, polimorfizmi i HLA, popullata shqiptare

INTRODUCTION

Autoimmune thyroid diseases (ATD), primarily Hashimoto's thyroiditis and Graves' disease, are among the most common autoimmune disorders and affect approximately 5–10% of the population worldwide (1). These diseases arise from a complex interplay between genetic susceptibility and environmental triggers that ultimately leads to immune-mediated damage or stimulation of thyroid tissue. Among the genetic determinants implicated in ATD, the human leukocyte antigen (HLA) region located on chromosome 6p21has been consistently identified as a major susceptibility locus (2). HLA molecules are responsible for antigen presentation to T lymphocytes and therefore play a central role in adaptive immune responses. Numerous studies have demonstrated associations between autoimmune thyroid diseases and specific HLA class II alleles**,** particularlyHLA-DR and HLA-DQ variants**,** which influence CD4+ T-cell activation and immune tolerance mechanisms (3). However, the distribution of HLA alleles varies considerably across ethnic groups and geographic regions.

Previous research has identified associations between autoimmune thyroid diseases and several HLA alleles in European, Asian, and Middle Eastern populations (4-6). Nevertheless, data from Balkan populations remain limited**,** and the immunogenetic background of autoimmune thyroid disease in this region is poorly characterized.

The aim of the present study was therefore toinvestigate the distribution of HLA class I and class II alleles in Albanian patients with autoimmune thyroid disease**.**

MATERIAL AND METHODS

Study design and populations

Study Population

This study involved 68 consecutive individuals diagnosed with Autoimmune thyroid disease (ATD) at the Endocrinology Unit of the University Hospital Center "Mother Teresa" between 2023 and 2025. Diagnosis of ATD disease was established based on clinical hyperthyroidism or hypothyroidism, altered serum thyroid-stimulating hormone (TSH), and positivity for TSH receptor antibodies (TRAb), thyroid peroxidase antibody AntiTPO and/or antithyroglobulin antibodies (AntiTg) 7,8. When feasible, thyroid ultrasound and scintigraphy findings were used to support the diagnosis.

Ethical approval

The study protocol received approval from the Ethics Committee of the University of Medicine of Tirana. Written informed consent was obtained from all participants before enrollment.

HLA genotyping

Genomic DNA was extracted from buffy coat samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Allele-level HLA genotyping of class I (HLA-A*, -B*, -C*) and class II (HLA-DRB1*, -DQB1*) loci was performed using PCR with sequence-specific primers (PCR-SSP) and Micro SSP™ DNA Typing Trays (One Lambda, Thermo Fisher Scientific, USA).

Data analysis

Allele frequencies were calculated through direct gene counting and reported as proportions. Quantitative independent variables with normal distribution across groups were tested using a Student t-test, with the null hypothesis that the variance is equal across groups being checked using Levene's test for equality of variance. All statistical analyses were performed using R software (R Foundation for Statistical Computing, version 4.3.1, R Core Team, 2023, Vienna, Austria).

RESULTS

Characteristics of the study sample populations

This study included 68 consecutive individuals diagnosed with ATD at the Endocrinology Unit at the University Hospital Center "Mother Teresa" between 2023 and 2025, comprising 51 patients with Hashimoto's thyroiditis (75.0%) and 17 patients with Graves' disease (25.0%). Mean age was 42.2 ± 11years while age distribution was normal across the entire patient cohort. Females predominated over males, 91% and 9% respectively.

HLA genotyping results

HLA allele distribution in autoimmune thyroid disease

HLA Class I

At the HLA-A locus, the most frequent allele was A*02:01, with an allele frequency of 38.0% (95% CI 29.4–47.4). Other common alleles included A*01:01 and A*24:02, each with a frequency of 9.9% (95% CI 5.7–16.5), followed by A*68:01 with 8.3% (95% CI 4.5–14.6) and A*03:01 with 7.4% (95% CI 3.8–13.7).

At the HLA-B locus, B*51:01 was the most frequent allele (16.2%, 95% CI 10.9–23.4), followed by B*18:01 (14.6%, 95% CI 9.6–21.6) and B*35:01 (13.8%, 95% CI 9.0–20.7).

At the HLA-C locus, C*07:01 was the predominant allele (22.3%, 95% CI 15.7–30.6), followed by C*12:03 (17.4%, 95% CI 11.8–24.8) and C*02:02 (10.7%, 95% CI 6.4–17.2),

Table 1. HLA allele frequencies in AITD patients

Locus	Allele	Frequency (%)	95% CI
HLA-A	A*02:01	38.0	29.4–47.4
	A*01:01	9.9	5.7–16.5
	A*24:02	9.9	5.7–16.5
	A*68:01	8.3	4.5–14.6
	A*03:01	7.4	3.8–13.7
HLA-B	B*51:01	16.2	10.9–23.4
	B*18:01	14.6	9.6–21.6
	B*35:01	13.8	9.0–20.7
HLA-C	C*07:01	22.3	15.7–30.6
	C*12:03	17.4	11.8–24.8
	C*02:02	10.7	6.4–17.2
HLA-DRB1	DRB1*11:01	26.6	19.7–34.9
	DRB1*16:01	18.8	12.9–26.7
	DRB1*04:01	12.5	7.8–19.4
HLA-DQB1	DQB1*03:01	35.5	27.5–44.4
	DQB1*05:02	19.4	13.6–26.8
	DQB1*02:01	12.1	7.7–18.5

HLA Class II

At the HLA-DRB1 locus, the most common allele was DRB1*11:01 with a frequency of 26.6% (95% CI 19.7–34.9), followed by DRB1*16:01 (18.8%, 95% CI 12.9–26.7) and DRB1*04:01 (12.5%, 95% CI 7.8–19.4).

At the HLA-DQB1 locus, DQB1*03:01 represented the most frequent allele (35.5%, 95% CI 27.5–44.4). This was followed by DQB1*05:02 (19.4%, 95% CI 13.6–26.8) and DQB1*02:01 (12.1%, 95% CI 7.7–18.5) (Table 1).

The most frequent alleles observed were HLA-A02:01, HLA-B51:01, HLA-C07:01, HLA-DRB111:01, and HLA-DQB1*03:01 (Fig. 1).

Comparison of HLA allele frequencies in Albanian ATD patients and other populations

When comparing the allele frequencies observed in the Albanian ATD cohort with previously published data from other populations (Table 2), several differences become apparent. The DRB1*11 allele showed a higher frequency in our cohort (26.6%) compared with most European populations, where frequencies typically range between 10–18% (9,10). Conversely, DRB1*03, a classical susceptibility allele for autoimmune thyroid disease in

Caucasian populations, appeared less frequent in the Albanian cohort (Table 2). These findings suggest that the immunogenetic background of autoimmune thyroid disease in Albania may differ from that observed in Northern European populations, possibly reflecting regional genetic variation within the Mediterranean and Balkan populations (Table 2) (3,4, 6).

Table 2. Comparison of HLA allele frequencies in Albanian ATD patients and other populations

Locus	**Allele**	**Albania ATD**	**Europe**	**Asia**
HLA-A	A*02	38%	25–35%	20–30%
HLA-B	B*51	16.2%	10–15%	<10%
HLA-C	C*07	22.3%	15–25%	10–15%
HLA-DRB1	DRB1*11	26.6%	10–18%	<10%
HLA-DRB1	DRB1*03	8.3%	20–30%	10–15%
HLA-DQB1	DQB1*03	35.5%	20–30%	15–25%
HLA-DQB1	DQB1*02	12.1%	20–30%	10–15%

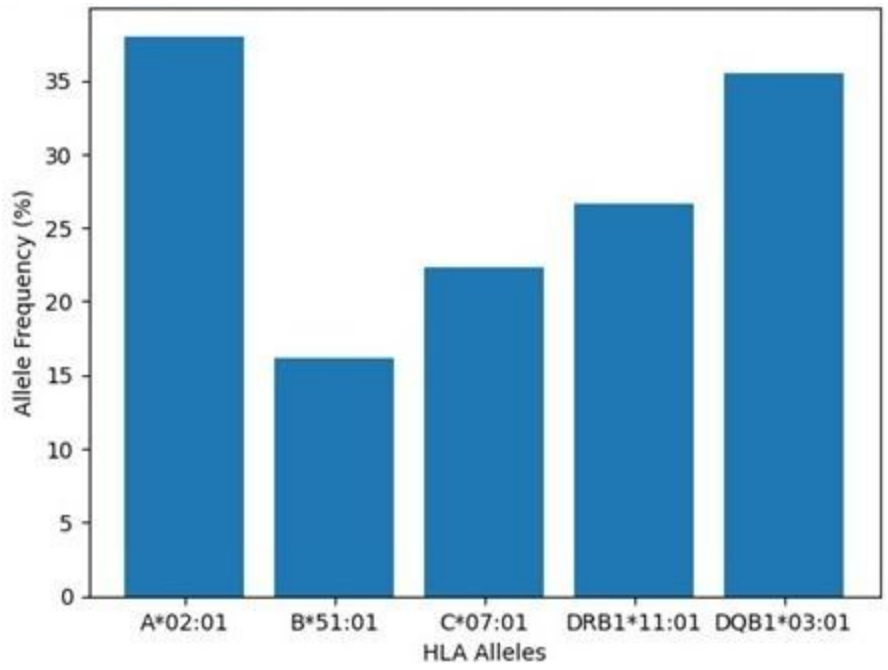


Figure 1. Most frequent HLA alleles in Albanian patients with Autoimmune Thyroid Disease.

DISCUSSION

Autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease, are among the most common autoimmune disorders worldwide and represent the leading cause

of thyroid dysfunction in iodine-sufficient regions (1). These diseases arise from a complex interaction between genetic predisposition and environmental triggers, ultimately leading to immune-mediated destruction or stimulation of thyroid tissue. Among the genetic factors involved, the human leukocyte antigen (HLA) region on chromosome 6p21 plays a critical role in determining individual susceptibility to autoimmune thyroid disease (2,3).

In the present study, we analyzed the distribution of HLA class I and class II alleles in Albanian patients with autoimmune thyroid disease. The most frequent alleles observed were HLA-A02:01, HLA-B51:01, HLA-C07:01, HLA-DRB111:01, and HLA-DQB1*03:01. These findings highlight the extensive polymorphism of the HLA region and support its involvement in autoimmune thyroid disease susceptibility.

Previous studies in European populations have frequently reported associations between autoimmune thyroid diseases and HLA class II alleles, particularly HLA-DRB103 and HLA-DQB102, which form the well-known DR3-DQ2 haplotype linked to Graves' disease (4). In contrast, the results of the present study showed a predominance of DRB111 and DQB103 alleles, suggesting a somewhat different immunogenetic profile in the Albanian population.

Interestingly, studies conducted in Mediterranean populations have reported similar findings. Research in Turkish cohorts demonstrated associations between autoimmune thyroid diseases and DRB1*11 as well as DQB1*03 alleles, indicating that these variants may contribute to disease susceptibility in this geographic region (5). The relatively high frequency of DRB1*11 and DQB1*03 observed in our cohort may therefore reflect shared genetic backgrounds within populations of the Eastern Mediterranean and Balkan regions.

At the HLA-DQB1 locus, DQB1*03:01 represented the most frequent allele in the present study. This finding is consistent with previous studies reporting increased frequencies of DQB1*03 alleles in autoimmune endocrine disorders, including autoimmune thyroid disease and type 1 diabetes (6). Because HLA-DQ molecules participate in antigen presentation to CD4+ T cells, structural differences in these molecules may influence the presentation of thyroid autoantigens and thereby contribute to disease development.

The present study also demonstrated relatively high frequencies of class I alleles, particularly A*02:01 and B*51:01. Although the role of class I HLA alleles in autoimmune thyroid diseases is less well established than that of class II alleles, increasing evidence suggests that CD8+ cytotoxic T cells may participate in thyroid tissue damage, especially in Hashimoto's thyroiditis (8). Class I molecules may therefore contribute to autoimmune processes through cytotoxic immune mechanisms directed against thyroid follicular cells.

Comparison of our findings with studies from other populations highlights the substantial geographic variability in HLA allele distribution. Studies from East Asian populations, for example, have reported associations between autoimmune thyroid disease and different HLA alleles, including specific DRB1 variants and certain class I alleles (6). Such differences underscore the importance of investigating the genetic architecture of autoimmune diseases in

specific populations, as susceptibility patterns may vary considerably according to ethnic background.

The present study provides the first characterization of HLA allele frequencies in Albanian patients with autoimmune thyroid disease. The allele distribution observed suggests that the Albanian population shares certain immunogenetic characteristics with other Mediterranean populations while also demonstrating distinctive features, particularly the relatively high frequency of DRB1*11 and DQB1*03 alleles.

Several limitations should be considered when interpreting these findings. First, the samplesize was relatively modest, which may limit the ability to detect associations involving less frequent alleles. Second, the present study focused on allele frequency analysis rather than haplotype structures, and further studies examining linkage disequilibrium and haplotype patterns may provide additional insight into the genetic susceptibility to autoimmune thyroid disease. Despite these limitations, the results contribute to the growing body of evidence supporting the role of HLA polymorphisms in autoimmune thyroid disease susceptibility. Future studies involving larger cohorts and multicenter collaborations within the Balkan region may help clarify the immunogenetic mechanisms underlying autoimmune thyroid diseases and improve our understanding of population-specific genetic risk factors.

CONCLUSION

This study represents the first analysis of HLA class I and class II allele frequencies in Albanian patients with autoimmune thyroid disease**.** The results demonstrate a predominance of HLA-A*02:01, HLA-B*51:01, HLA-C***07***:01, HLA-DRB1*11:01, and HLA-DQB1*03:01, highlighting the considerable polymorphism of the HLA region within this population. The allele distribution observed in the present cohort shows partial similarities with other Mediterranean populations but also suggests distinctive immunogenetic characteristics in the Albanian population. Further studies involving larger cohorts and comparative analyses across different populations are needed to confirm these observations and to clarify the contribution of HLA variation to the pathogenesis of autoimmune thyroid diseases.

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Conflict of interest: Nothing to declare

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CLINICO-PATHOLOGICAL CHARACTERISTICS OF GASTRIC CANCER PATIENTS

Bledi Kreka [1,2], Martiola Kola[1], Dea Kreka[1],Drini Shehi[2], Arvit Llazani[2], Ervin Toci[1],Manika Kreka[1,2],Arvin Dibra[1,2]

[1]University of Medicine, Tirana, Albania

[2]Department of Oncology, University Hospital Center "Mother Teresa", Tirana, Albania

Corresponding E-mail: manika.kreka@umed.edu.al

ABSTRACT

Background: Gastric cancer remains a major global health burden, with significant geographic variability in incidence and histopathological patterns. Understanding clinicopathological characteristics is essential for improving diagnosis and management. This study aimed to evaluate the demographic, histopathological, and clinical characteristics of patients diagnosed with gastric cancer in a tertiary care setting.

Methods: A retrospective observational study was conducted using a structured database of gastric cancer patients. Variables included age, sex, family history, histopathological subtype, signet ring cell presence, TNM staging, lymph node involvement, and treatment modalities. Descriptive and comparative statistical analyses were performed. This study used the data of patients in the 2023-2025 period.

Results: A total of 221 patients were included, with a mean age of 64.0 ± 9.9 years. Male predominance was observed (71.5%). Diffuse (48.9%) and intestinal (47.5%) histological subtypes were nearly equally distributed. Signet ring cell carcinoma was present in 8.7% of cases. Among the 183 patients with complete staging data, most presented with advanced local disease, with the T3 stage being the most frequent (60.1%), and nodal involvement (N2-N3) was observed in a significant proportion. Distant metastases were identified in 17.2 % of patients at diagnosis.

Conclusions: Gastric cancer in this cohort is characterized by late-stage presentation and significant nodal involvement. The nearly equal distribution of histological subtypes highlights the heterogeneity of the disease. Early detection strategies and improved diagnostic pathways are essential to optimize patient outcomes.

Keywords: Gastric cancer, TNM staging, histopathology, signet ring cells, lymph node involvement

KARAKTERISTIKAT KLINIKO-PATOLOGJIKE TË PACIENTËVE ME KANCER GASTRIK

ABSTRAKT

Hyrja. Kanceri gastrik mbetet një barrë e rëndësishme globale për shëndetin publik, me variabilitet të konsiderueshëm gjeografik në incidencë dhe modele histopatologjike. Të kuptuarit e karakteristikave kliniko-patologjike është thelbësor për përmirësimin e diagnostikimit dhe menaxhimit të kësaj sëmundjeje. Ky studim synoi të vlerësojë karakteristikat demografike, histopatologjike dhe klinike të pacientëve të diagnostikuar me kancer gastrik në një qendër të kujdesit terciar.

Metodologjia. Një studim retrospektiv observacional u krye duke përdorur një bazë të dhënash të strukturuar për pacientët me kancer gastrik. Variablat e përfshira ishin: mosha, gjinia, historia familjare, nëntipet histopatologjike, prania e qelizave unazore me mukus (signet ring cells), stadifikimi TNM, përfshirja e limfonodujve dhe modalitetet terapeutike. U kryen analiza statistikore përshkruese dhe krahasuese. Në studim u përfshinë të dhënat e pacientëve të trajtuar gjatë periudhës 2023–2025.

Rezultatet. Gjithsej u përfshinë 221 pacientë, me moshë mesatare 64.0 ± 9.9 vjeç. U vërejt mbizotërim i gjinisë mashkullore (71.5%). Nëntipet histologjike difuze (48.9%) dhe intestinale (47.5%) ishin të shpërndara pothuajse njëlloj. Karcinoma me qeliza unazore me mukus ishte e pranishme në 8.7% të rasteve. Ndër 183 pacientët me të dhëna të plota të stadifikimit, shumica paraqiteshin me sëmundje lokale të avancuar, ku stadi T3 ishte më i shpeshti (60.1%), dhe përfshirja e limfonodujve (N2-N3) u vu re në një proporcion të konsiderueshëm. Metastazat në distancë u identifikuan në 17.2% të pacientëve në momentin e diagnostikimit.

Përfundimet. Kanceri gastrik në këtë kohortë karakterizohet nga paraqitja në stade të vonshme dhe prekje e konsiderueshme e limfonodujve. Shpërndarja pothuajse e barabartë e nëntipeve histologjike nënvizon heterogjenitetin e kësaj sëmundjeje. Strategjitë e zbulimit të hershëm dhe rrugët diagnostike të përmirësuara janë thelbësore për optimizimin e rezultateve të pacientëve.

Fjalë kyç: Kancer gastrik, stadifikimi TNM, histopatologji, qeliza unazore me mukus, limfonoduj

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, despite a gradual decline in incidence in certain regions. According to recent global estimates, it continues to represent a significant public health burden, particularly in low- and middle-income countries where early detection strategies are limited [1, 2]. The disease is often diagnosed at advanced stages due to its insidious onset and non-specific early symptoms, which significantly complicates management and worsens clinical outcomes [3].

Histopathologically, gastric cancer is a heterogeneous disease. The Lauren classification divides it into intestinal and diffuse subtypes, which differ in epidemiology, pathogenesis, and

clinical behavior. The intestinal type is typically associated with environmental factors and follows a stepwise progression, whereas the diffuse type is more often linked to genetic predisposition and tends to present at a more advanced stage [4, 5].
Tumor staging, particularly the TNM classification, remains fundamental in determining disease extent and guiding therapeutic decisions. Lymph node involvement and the presence of distant metastases are key indicators of disease progression and are associated with more aggressive disease and poorer prognosis [6, 7].
Given these considerations, a comprehensive evaluation of clinicopathological characteristics at diagnosis is essential to better understand disease patterns and improve diagnostic strategies. This study aims to analyze demographic, histopathological, and staging characteristics of gastric cancer patients in a tertiary care setting.

MATERIAL AND METHODS

This study was designed as a retrospective observational analysis, aiming to provide a detailed evaluation of the clinicopathological characteristics of patients diagnosed with gastric cancer.
The primary aim of the study was to assess the distribution of disease stages at diagnosis. Secondary objectives included the evaluation of demographic characteristics, histopathological subtypes, lymph node involvement, the presence of signet ring cells, and treatment-related variables. All data were handled in accordance with applicable institutional and national ethical standards. Given the retrospective nature of the study and the use of anonymized clinical data, individual informed consent was waived.
Data were collected from a structured clinical database including 221 patients diagnosed with gastric cancer. The dataset contained detailed information on patient demographics such as age and sex, tumor-related variables including histological subtype and TNM staging, and additional pathological features such as the presence of signet ring cells.
Patients were included if they had a confirmed diagnosis of primary gastric cancer and complete clinicopathological data. Patients with incomplete records or non-epithelial gastric malignancies were excluded from the analysis.
The primary endpoint of the study was the distribution of TNM staging at the time of diagnosis. Secondary endpoints included histopathological subtype distribution, degree of lymph node involvement, and presence of signet ring cell carcinoma.
Statistical analysis was primarily descriptive. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The analysis was conducted using standard statistical tools, ensuring accurate summarization of the dataset.

RESULTS

The study population consisted of a total of 221 patients diagnosed with gastric cancer, representing the full cohort included in the analysis.

The mean age of the patients was 64.0 ± 9.9 years, indicating that the majority of individuals were within an older age group. The relatively narrow standard deviation suggests that most patients were clustered around this mean value, with limited variability in age distribution.
Regarding sex distribution, a clear predominance of male patients was observed. Males accounted for 158 cases, corresponding to 71.5% of the total population, whereas females comprised 63 cases, representing 28.5%. This indicates that more than two-thirds of the study population were male, while less than one-third were female.

Table 1. Demographic Characteristics of the Study Population

Variable	**Value**
Total patients	221
Mean age	64.0 ± 9.9 years
Male	158 (71.5%)
Female	63 (28.5%)

Overall, the data demonstrate that within this cohort, gastric cancer was more frequently observed in male patients and was predominantly diagnosed in individuals in their seventh decade of life.

Table 2. Histopathological Distribution of Gastric Cancer (based on Lauren classification)

Histological Type	**n (%)**
Diffuse	107 (48.9%)
Intestinal	104 (47.5%)
Mixed	10 (3.6%)

The distribution of histopathological subtypes within the study population demonstrates a relatively balanced pattern between the two main categories of gastric cancer. The diffuse type was identified in 107 patients, accounting for 48.9% of cases, while the intestinal type was present in 104 patients, representing 47.5% of the cohort. This indicates that both subtypes were almost equally represented in the analyzed population.
In contrast, mixed tumors constituted a small proportion of cases, with only 10 patients (3.6%). This finding suggests that, within this dataset, most tumors were classified under the main histological categories rather than being grouped as mixed tumors.
Overall, the data reflect a near-equal distribution between diffuse and intestinal histological types, with a minimal contribution from mixed type in this cohort.

Table 3. Presence of Signet Ring Cells

Status	**n (%)**
Present	19 (8.6%)
Absent	202 (91.4%)

The presence of signet ring cells was evaluated in the study cohort. Only 19 patients (8.6%) demonstrated the presence of signet ring cells, whereas the vast majority, 202 patients (91.4%), did not exhibit these cells. These findings indicate that signet ring cells were relatively uncommon within the studied population. The presence of signet ring cells was identified in a relatively small proportion of patients. Although less frequent, this histological feature is clinically significant due to its association with more aggressive tumor behavior and diffuse-type gastric cancer. Its relatively low prevalence in this cohort is consistent with contemporary epidemiological data.

Table 4. Distribution of Tumor (T Stage)

Stage	**n**	**%**
T1	5	2.7%
T2	20	10.9%
T3	110	60.1%
T4	48	26.2%
Total	183	100%

The distribution of T stage demonstrates a clear predominance of advanced tumor invasion at diagnosis. The majority of patients were classified as T3 (60.1%), indicating tumor penetration into the subserosa, followed by T4 (26.2%), which reflects invasion into adjacent structures. In contrast, early-stage tumors (T1–T2) accounted for only 13.6% of cases combined.

This pattern strongly suggests delayed diagnosis and aligns with the well-established natural history of gastric cancer, where early stages are often asymptomatic and therefore underdiagnosed. The low proportion of T1 tumors (2.7%) further highlights the lack of effective early detection strategies in the studied population.

Most patients presented with advanced tumor invasion, with T3 being the most common stage. This indicates that most tumors had already penetrated the muscularis propria or beyond at the time of diagnosis. The low number of early-stage tumors (T1–T2) further emphasizes the issue of delayed diagnosis.

Table 5. Lymph Node Involvement (N Stage)

Stage	**N**	**%**
N0	39	17,6%
N1	41	18,6%
N2	54	24,5%
N3	49	22,2%
Total	183	100%

The distribution of lymph node involvement indicates a substantial burden of regional disease at the time of diagnosis. While 17,6 % of patients had no nodal involvement (N0), the majority (65,3% %) presented with positive lymph nodes (N1-N3). Notably, advanced nodal stages (N2 and N3) were present in 46,7 % of cases, reflecting extensive regional spread.
This pattern underscores the aggressive nature of gastric cancer and its tendency for early lymphatic dissemination. The high prevalence of N2–N3 stages is clinically significant, as it is strongly associated with more advanced disease, influences staging classification, and directly impacts therapeutic decision-making, including the need for systemic therapy in addition to surgical management.

Table 6. Distant Metastasis (M Stage)

Stage	**n (%)**
M0	173 (80.1 %)
M1	43 (19.9 %)

Distant metastasis was assessed according to the M stage classification. The majority of patients, 173 (80.1%), were categorized as M0, indicating the absence of distant metastasis, while 43 patients (19.9%) were classified as M1, reflecting the presence of distant metastatic disease. These results demonstrate that most patients in the cohort did not have distant metastases at the time of evaluation. Nearly one-fifth of patients presented with distant metastases at diagnosis. This is a clinically important observation, as metastatic disease significantly limits treatment options and reflects late-stage detection.

DISCUSSION

The present study provides a comprehensive evaluation of the clinicopathological characteristics of gastric cancer patients in a tertiary care setting, highlighting key patterns related to demographic distribution, histopathological subtypes, and tumor staging at diagnosis. The findings confirm that gastric cancer continues to be predominantly diagnosed

at advanced stages, reflecting a persistent global challenge in early detection and timely diagnosis.

One of the most prominent findings of this study is the predominance of advanced tumor stages at presentation, with the majority of patients classified as T3 or T4. This observation is consistent with contemporary literature, which indicates that gastric cancer is frequently asymptomatic in its early stages and therefore often diagnosed only after significant local invasion has occurred [3, 7]. The low proportion of early-stage tumors (T1-T2) in this cohort underscores the absence or limited implementation of effective screening strategies, particularly in healthcare systems where routine endoscopic surveillance is not widely available.

The demographic distribution observed in this study, with a clear male predominance and a mean age in the sixth decade of life, aligns with global epidemiological trends. Previous studies have consistently reported higher incidence rates among males, which may be attributed to differences in environmental exposures, lifestyle factors such as smoking and diet, and potential hormonal influences [2]. The age distribution further supports the well-established association between gastric cancer and advancing age, reflecting the cumulative effect of carcinogenic exposures over time.

A particularly noteworthy finding in this study is the nearly equal distribution between diffuse and intestinal histopathological subtypes. This contrasts with several reports from Western populations, where the intestinal type is more prevalent [5]. The balanced distribution observed in this cohort may suggest regional variations in etiological factors, including Helicobacter pylori prevalence, dietary habits, and genetic predisposition. The diffuse type, which is often associated with a more aggressive clinical course and poorer differentiation, may contribute to the advanced stage at diagnosis observed in this population [4].

The presence of signet ring cell carcinoma, although relatively low in frequency, remains clinically significant. This subtype is typically associated with diffuse-type gastric cancer and is characterized by rapid progression and a tendency for peritoneal dissemination. Its identification, even in a minority of patients, is important due to its implications for prognosis and treatment planning [2].

Lymph node involvement represents another critical aspect highlighted by this study. A substantial proportion of patients were classified as N2 or N3, indicating extensive regional spread. This finding is of particular clinical importance, as nodal status is a key determinant in staging and directly influences therapeutic decisions, including the extent of surgical resection and the need for adjuvant or neoadjuvant therapy [6]. The high rate of lymph node involvement further supports the observation that gastric cancer is frequently diagnosed at an advanced stage, when regional dissemination has already occurred.

The proportion of patients presenting with distant metastases (approximately 20%) is also consistent with previously reported data. Although this figure may appear moderate compared to some global estimates, it nevertheless reflects a significant burden of advanced disease at diagnosis. Metastatic involvement drastically limits curative treatment options and necessitates a shift toward palliative management strategies, emphasizing the importance of early detection [7].

When interpreting these findings, it is important to consider the broader context of healthcare access and diagnostic infrastructure. In many regions, limited access to endoscopic evaluation and delayed referral pathways contribute to late-stage diagnosis. This underscores the need for systemic improvements, including increased awareness, implementation of screening programs in high-risk populations, and better integration of diagnostic services.

Furthermore, the heterogeneity observed in histopathological subtypes and staging patterns highlights the complex biological nature of gastric cancer. Recent advances in molecular classification have demonstrated that gastric cancer is not a single disease entity but rather a group of biologically distinct subtypes with different clinical behaviors and therapeutic responses [3]. Although molecular data were not included in this study, integrating such information in future research could provide deeper insights into disease mechanisms and guide personalized treatment approaches.

Overall, the findings of this study are in line with current global evidence and reinforce the need for improved strategies in early diagnosis and disease management. The predominance of advanced-stage disease, significant lymph node involvement, and histopathological heterogeneity collectively highlight the ongoing challenges in the management of gastric cancer.

This study has several limitations that should be considered when interpreting the results. The retrospective design may introduce selection bias, and the use of a single-center database may limit the generalizability of the findings. Additionally, some variables had incomplete data, which may affect the accuracy of certain analyses. The absence of survival analysis, although intentional, limits the ability to correlate clinicopathological features with outcomes.

Future studies should focus on prospective multicenter designs to validate these findings in larger populations. There is also a need to integrate molecular and genetic profiling to better understand disease heterogeneity. Furthermore, the implementation of screening programs and improved access to diagnostic tools could significantly enhance early detection and improve patient outcomes.

CONCLUSIONS

This study demonstrates that gastric cancer is predominantly diagnosed at advanced stages, with significant tumor invasion and lymph node involvement at presentation. The balanced distribution of histopathological subtypes reflects the biological heterogeneity of the disease. These findings emphasize the urgent need for improved early detection strategies and optimized diagnostic approaches.

Conflict of interest: Nothing to declare

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ORIGINAL ARTICLE

FACTORS INFLUENCING HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH DIABETIC NEPHROPATHY: A CROSS-SECTIONAL STUDY

Nevi Pasko[1], Teuta Dedej[2], Elvana Rista[3], Ariana Strakosha[1], Alba Xhoku[1], Vilma Cadri[1], Amantia Imeraj[1]

[1]Service of Nephrology Dialysis and Transplantation. University Hospital Center "Mother Teresa" Tirana, Albania

[2]Department of Laboratory, University Hospital Center "Mother Teresa" Tirana, Albania

[3]Service of Nephrology, Hygeia Hospital, Tirana, Albania

Corresponding E-Mail: nevipasko@hotmail.com

ABSTRACT

Introduction. Diabetic nephropathy is a leading cause of chronic kidney disease (CKD) and is associated with significant morbidity. Beyond traditional clinical outcomes, health-related quality of life (HRQoL) has emerged as an important patient-centered measure.

Objectives. The study aimed to evaluate health-related quality of life (HRQoL) in patients with diabetic nephropathy using the KDQOL-36 questionnaire and to identify the clinical and laboratory factors associated with its impairment.

Material and Methods. This cross-sectional study included 105 patients with diabetic nephropathy. HRQoL was assessed using the KDQOL-36 questionnaire. Demographic, clinical, and laboratory data were collected, and multivariable regression analyses were performed to identify factors associated with impaired HRQoL.

Results. The majority of patients reported moderate to poor HRQoL across all domains. Physical functioning, mental health, and disease burden were particularly affected. Advanced CKD stages (4–5) (aOR 3.45, 95% CI: 1.74–6.83) and dialysis (aOR 3.10, 95% CI: 1.52–6.30) were strongly associated with poor overall HRQoL. Additional predictors included ≥2 comorbidities (aOR 2.30), duration of diabetic nephropathy >10 years (aOR 2.05), and age >70 years (aOR 2.00). Among laboratory variables, anemia (hemoglobin <10 g/dL; aOR 3.25) was the strongest predictor, followed by poor glycemic control (HbA1c ≥9%; aOR 3.05), elevated creatinine (≥3.5 mg/dL; aOR 2.95), hypoalbuminemia (<3.0 g/dL; aOR 2.70), and elevated C-reactive protein (CRP >50 mg/L; aOR 2.60).

Conclusions. HRQoL is significantly impaired in patients with diabetic nephropathy and is influenced by multiple clinical and laboratory factors. These findings highlight the need for comprehensive, patient-centered management strategies targeting metabolic control, anemia, inflammation, and disease burden to improve overall patient outcomes.

Keywords: Diabetic nephropathy, health-related quality of life, KDQOL-36

FAKTORËT QË NDIKOJNË NË CILËSINË E JETËS SË LIDHUR ME SHËNDETIN, TE PACIENTËT ME NEFROPATI DIABETIKE: NJË STUDIM CROSS-SECTIONAL

ABSTRAKT

Hyrje. Nefropatia diabetike është një nga shkaqet kryesore të sëmundjes kronike të veshkave (SKV) dhe shoqërohet me rritje të sëmundshmërisë. Përveç faktorëve tradicionale që ndikojnë në ecurinë e pacientëve, vlerësimi i cilësisë së jetës është një parametër i rëndësishëm i vleresimit të pacientit.

Objektivat. Qëllimi i studimit ishte të vlerësojë cilësinë e jetës tek pacientët me nefropati diabetike duke përdorur pyetësorin KDQOL-36, si dhe të identifikojë faktorët klinikë dhe laboratorikë të lidhur me cilësinë e jetës.

Materiali dhe Metodat. Në studim u përfshinë 105 pacientë me nefropati diabetike. Cilvsia e jetës u vlerësua duke përdorur pyetësorin KDQOL-36. U mblodhën të dhëna demografike, klinike dhe laboratorike, dhe u kryen analiza regresioni multivariat për të identifikuar faktorët që ndikojnë në cilësinë e jetës.

Rezultatet. Shumica e pacientëve raportuan cilësi të jetës mesatare deri të dobët në të gjitha dimensionet. Veçanërisht të prekur ishin funksioni fizik, shëndeti mendor dhe barra e sëmundjes. Pacientët ne stadet e avancuara të SKV (4–5) (OR 3.45, CI 95%: 1.74–6.83) dhe apo në dializë (OR 3.10, CI 95%: 1.52–6.30) u karakterizuan nga cilësi më të dobët të jetës. Faktorë të tjerë që ndikonin ishin prania e ≥2 komorbiditete (OR 2.30), kohëzgjatja e nefropatisë diabetike >10 vjet (OR 2.05) dhe mosha >70 vjeç (OR 2.00). Ndër parametrat laboratorikë që u vlerësuan, anemia (hemoglobina <10 g/dL; OR 3.25) ishte prediktori më i fortë, ndjekur nga kontrolli i dobët glicemik (HbA1c ≥9%; aOR 3.05), kreatinina e lartë (≥3.5 mg/dL; OR 2.95), hipoalbuminemia (<3.0 g/dL; OR 2.70) dhe proteina C-reaktive e lartë (CRP >10 mg/L; OR 2.60).

Përfundime. Cilësia e jetës është e dëmtuar ndjeshëm tek pacientët me nefropati diabetike dhe ndikohet nga faktorë të shumtë klinikë dhe laboratorikë. Këto gjetje theksojnë nevojën për strategji gjithëpërfshirëse dhe të orientuara drejt pacientit, që synojnë përmirësimin e kontrollit metabolik, menaxhimin e anemisë dhe inflamacionit, me qëllim reduktimin e barrës së sëmundjes për të përmirësuar rezultatet e përgjithshme të pacientëve.

Fjalë kyç. Nefropatia diabetike, cilësia e jetës e lidhur me shëndetin, KDQOL-36.

INTRODUCTION

Diabetes mellitus represents a major global health burden and remains the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide (1,2,3,29). The increasing prevalence of type 2 diabetes has been accompanied by a growing incidence of diabetic kidney disease (DKD), one of the most severe microvascular complications and a major contributor to morbidity and mortality (4,5,6). Despite advances in glycemic control and the introduction of renoprotective therapies, including SGLT2 inhibitors, a substantial proportion of patients continue to progress toward CKD and require renal replacement therapy (7,8).

Beyond its clinical manifestations, DKD has a profound impact on patients' daily functioning and well-being. Individuals with diabetes and CKD frequently experience fatigue, reduced functional capacity, and psychological distress, all of which contribute to impaired health-related quality of life (HRQoL) (9,10). Importantly, reduced HRQoL has been associated with adverse clinical outcomes, including increased hospitalization, poor treatment adherence, accelerated disease progression, and higher mortality (11,12).

According to the World Health Organization (WHO), quality of life (QoL) is defined as an individual's perception of their position in life within the context of their cultural and social environment (13). This concept emphasizes the multidimensional nature of QoL, encompassing physical, psychological, and social domains, which are significantly affected in chronic diseases such as diabetes and CKD.

HRQoL assessment has therefore become an essential component of patient-centered care (14,19). The KDQoL™-36 questionnaire is a validated instrument widely used in CKD populations, combining generic and disease-specific domains to provide a comprehensive evaluation of patient well-being (15-17). Its practicality supports its use in both clinical practice and research settings.

This study aimed to evaluate HRQoL in patients with diabetic nephropathy using the KDQOL-36 questionnaire and to identify the clinical, demographic, and laboratory factors associated with its impairment.

MATERIALS AND METHODS

Study population

The study population consisted of 105 patients diagnosed with diabetic nephropathy based on established clinical and laboratory criteria, who were admitted to the Nephrology or Endocrinology Service at the University Hospital Center "Mother Teresa". The inclusion criteria for the study were adult patients with type 2 diabetes mellitus and a confirmed diagnosis of diabetic nephropathy, with complete clinical data and fully complete questionnaires. Exclusion criteria included patients with kidney injury unrelated to diabetes, incomplete laboratory or clinical data, and those who declined to participate in the quality-of-life assessment. All participants were informed about the purpose of the study and provided written informed consent prior to participation. Participation was voluntary, and the confidentiality and anonymity of patient data were maintained throughout the study.

Measures and data collections

Data were collected from medical records and through the administration of the KDQOL-36 questionnaire. For each patient, demographic variables (age, sex, and place of residence) were recorded, along with disease-related characteristics and additional chronic comorbidities were also documented. Laboratory parameters included glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, serum albumin, total protein, urea, creatinine,

complete blood count, and C-reactive protein (CRP). In addition, data regarding the need for renal replacement therapy were collected. The KDQOL-36 questionnaire was administered to all participants in accordance with standardized procedures, ensuring completeness and reliability of responses. The original scores were linearly converted to a range of 0–100. A high score represents better HRQoL.

Statistical analysis

The collected data were processed and analyzed using standard statistical software (IBM SPSS Statistics, version 27). Descriptive statistics were used to summarize the variables, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

To evaluate associations between clinical, laboratory, and HRQoL variables, statistical tests were applied as appropriate. The chi-square (χ^2) test was used for comparisons between categorical variables, while continuous variables were analyzed using the independent samples t-test or the Mann–Whitney U test, depending on data distribution. Analysis of variance (ANOVA) was performed for comparisons across multiple groups. Multivariable linear and logistic regression analyses were conducted to identify independent predictors of HRQoL outcomes. Statistical significance was defined as a two-tailed p-value < 0.05.

RESULTS

Demographic and disease-related characteristics of patients

The study population included 105 patients with diabetic nephropathy. The majority of patients were aged between 61-70 years (29.5%), followed by those aged 51–60 years (25.7%), while only 8.6% were ≤40 years (Table 1). Males predominated (58.1%), and most participants resided in urban areas (62.9%). The duration of diabetes was most commonly 11–15 years (33.3%), followed by >15 years (29.5%), indicating a predominantly long-standing disease course.

In terms of kidney disease, 44.8% of patients had a known disease duration of less than 5 years, while 19.0% had a duration exceeding 10 years. The distribution of CKD stages showed a predominance of advanced disease, 78.2% of patients in stages 3–5 with stage 4 being the most frequent (30.5%).

Comorbidities were highly prevalent, with 46.7% of patients presenting with two or more chronic conditions, while only 13.3% had no comorbidities. Regarding renal replacement therapy, 34.3% of patients were undergoing dialysis.

Table 1. Demographic, clinical, and disease-related characteristics of the study population (n = 105)

Variable	Category	n (%)
Age (years)	Mean ± SD	58.6 ± 12.4
	≤40	9 (8.6)
	41–50	19 (18.1)
	51–60	27 (25.7)
	61–70	31 (29.5)
	>70	19 (18.1)
Sex	Male	61 (58.1)
Residence	Urban	66 (62.9)
Duration of diabetes (years)	Mean ± SD	12.3 ± 6.8
	≤5	13 (12.4)
	6–10	26 (24.8)
	11–15	35 (33.3)
	>15	31 (29.5)
Duration of diabetic nephropathy (years)	Mean ± SD	6.7 ± 4.5
	<5	47 (44.8)
	5–10	38 (36.2)
	>10	20 (19.0)
CKD stage	Stage 1	7 (6.7)
	Stage 2	16 (15.2)
	Stage 3	28 (26.7)
	Stage 4	32 (30.5)
	Stage 5	22 (21.0)
Comorbidities	None	14 (13.3)
	One	42 (40.0)
	≥2	49 (46.7)
Renal replacement therapy	Dialysis	46 (44.8)

CKD: chronic kidney disease. Data are presented as mean ± standard deviation (SD) or n (%), as appropriate.

Laboratory findings of patients

The majority of patients had HbA1c levels ≥9.0% (42.9%), while 36.2% were in the range of 7.0–8.9%, and 21.0% had HbA1c <7.0%. Normal serum albumin levels (≥3.5 g/dL) were observed in 25.7% of patients, whereas hypoalbuminemia was present in 74.3%, including mild (29.5%), moderate (26.7%), and severe (18.1%) forms. Total serum protein levels were 6.0–6.9 g/dL in 37.1% of patients and 7.0–7.9 g/dL in 33.3%, while 20.0% had levels <6.0 g/dL and 9.5% had levels ≥8.0 g/dL. Anemia was common, with 27.6% of patients having

hemoglobin <10 g/dL and 39.0% within 10.0–11.9 g/dL; only 8.6% had hemoglobin ≥14 g/dL.

Evaluation of the quality of life of patients

Table 2 presents the distribution of KDQOL-36 scores across its main domains, including physical functioning, mental health, symptom burden, effects of kidney disease on daily life, and perceived burden of disease, as well as the overall score. The results are categorized into four levels (poor, moderate, good, and very good) based on a 0–100 scoring system, and expressed as frequencies and percentages.

Table 2. Quality of life of study participants.

QoL Domain	0–39 (poor)	40–59 (moderate)	60–79 (good)	80–100 (very good)
Physical Functioning	28 (26.7)	39 (37.1)	27 (25.7)	11 (10.5)
Psychological Well-being	25 (23.8)	36 (34.3)	29 (27.6)	15 (14.3)
Symptoms / Problems	20 (19.0)	33 (31.4)	34 (32.4)	18 (17.1)
Effects of Kidney Disease on Daily Life	31 (29.5)	42 (40.0)	23 (21.9)	9 (8.6)
Burden of Kidney Disease	34 (32.4)	38 (36.2)	22 (21.0)	11 (10.5)
Overall KDQOL-36 Score	29 (27.6)	40 (38.1)	25 (23.8)	11 (10.5)

KDQOL-36: Kidney Disease Quality of Life-36 questionnaire. Data are presented as n (%). Higher scores indicate better health-related quality of life. Score categories: 0–39 (poor), 40–59 (moderate), 60–79 (good), 80–100 (very good).

Physical functioning was rated as very good (≥80) in only 10.5% of patients and good (60–79) in 25.7%, while the majority reported moderate (40–59; 37.1%) or poor (≤39; 26.7%) levels. Mental health showed a similar pattern, with 14.3% reporting very good and 27.6% good emotional well-being, compared to 34.3% moderate and 23.8% poor scores. Regarding symptoms, 17.1% of patients reported very good and 32.4% good status, whereas 31.4% and 19.0% experienced moderate and poor symptom burden, respectively. The impact of kidney disease on daily life was considerable, with 40.0% and 29.5% of patients reporting moderate and poor levels, respectively, and only 21.9% achieving good or very good scores. Similarly, a high disease burden was reported, with 32.4% of patients in the poor category and 36.2% in the moderate category, while only 31.5% reported good or very good outcomes. Overall, only 10.5% of patients had very good quality of life and 23.8% good quality, whereas the majority were classified as moderate (38.1%) or poor (27.6%).

Multiple linear regression models were applied to see which factors influence the different components of the KDQoL-36. The graph in Fig 1 illustrates the association between selected clinical variables and the KDQOL-36 total score, presented as adjusted odds ratios (ORs)

with 95% confidence intervals, where values above 1 indicate a higher likelihood of impaired quality of life.

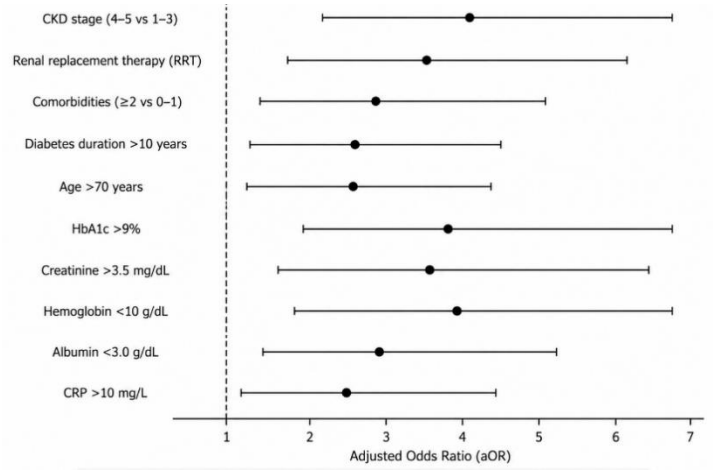


Figure. 1. Association between KDQOL-36 total score and laboratory findings.

The data demonstrates the cumulative impact of several laboratory factors on quality of life. HbA1c ≥9% (OR 3.05) and creatinine ≥3.5 mg/dL (OR 2.95) were strong indicators of poor quality of life, highlighting the importance of metabolic control and renal function. Anemia (hemoglobin <10 g/dL) emerged as the strongest overall predictor (OR 3.25), consistently affecting multiple domains. Hypoalbuminemia <3.0 g/dL (OR 2.70) and elevated CRP >50 mg/L (OR 2.60) further reinforced this pattern, suggesting that quality of life in diabetic nephropathy is influenced by a complex interplay of metabolic, nutritional, and inflammatory factors.

The overall quality of life score was significantly influenced by CKD stages 4–5 (OR 3.45, 95% CI: 1.74–6.83) and dialysis (OR 3.10, 95% CI: 1.52–6.30), indicating that disease progression and renal replacement therapy are major determinants of poor QoL. Additionally, the presence of ≥2 comorbidities (OR 2.30, 95% CI: 1.17–4.52), duration of diabetic nephropathy >10 years (OR 2.05, 95% CI: 1.02–4.12), and age >70 years (OR 2.00, 95% CI: 1.00–3.98) were also associated with worse overall QoL.

These findings suggest that quality of life in patients with diabetic nephropathy is multifactorial, reflecting not only the role of CKD progression but also the cumulative burden of comorbidities, treatment-related factors, and demographic characteristics.

DISCUSSION

The present study demonstrates that health-related quality of life (HRQoL) is markedly impaired in patients with diabetic nephropathy, with the majority of participants reporting moderate to poor scores across all KDQOL-36 domains. These findings are consistent with previous studies indicating that CKD, particularly in the context of diabetes, significantly compromises physical, psychological, and social well-being (15,17). The observed

impairment in physical functioning and mental health in our cohort is in line with prior research showing that HRQoL declines progressively with advancing CKD stages and worsens further after the initiation of dialysis (16,17). This deterioration likely reflects the combined effects of uremic symptoms, reduced physical capacity, and the burden of long-term disease management. Symptom burden, including fatigue, pain, and sleep disturbances, has been consistently identified as a key determinant of reduced HRQoL in CKD populations (18). A central finding of this study is the strong association between advanced CKD (stages 4–5) and dialysis with poor overall quality of life. These results are consistent with previous evidence indicating that disease progression and renal replacement therapy are major predictors of HRQoL impairment (16,17). Although dialysis is life-sustaining, it imposes substantial physical and psychosocial constraints, including treatment-related fatigue, time dependency, and reduced social participation (20).

In addition, our findings highlight the impact of comorbidities, disease duration, and age on HRQoL. Patients with multiple comorbidities and longer duration of diabetic nephropathy were more likely to report poorer quality of life, reflecting the cumulative burden of chronic disease. These observations are consistent with previous studies identifying multimorbidity and aging as key determinants of HRQoL in CKD populations (21,16). Importantly, laboratory parameters emerged as strong predictors of HRQoL impairment. Poor glycemic control (HbA1c ≥9%) and reduced renal function (elevated creatinine) were significantly associated with worse outcomes, supporting the established role of metabolic and renal dysfunction in disease progression (22,23). Anemia was identified as the strongest predictor across multiple domains, in agreement with previous reports linking anemia to fatigue, reduced exercise tolerance, and diminished quality of life in CKD patients (24). Furthermore, hypoalbuminemia and elevated CRP were independently associated with poorer HRQoL, demonstrating the role of nutritional status and chronic inflammation. These findings support the concept that HRQoL in diabetic nephropathy is influenced by a complex interplay of metabolic, nutritional, and inflammatory factors, as previously described in CKD populations (25,26).

This study has several limitations that should be considered when interpreting the findings. First, the single-center design may limit the generalizability of the results to broader populations. Second, the cross-sectional nature of the study does not allow for the establishment of causal relationships between clinical variables and health-related quality of life (HRQoL). Third, the relatively small sample size may reduce the statistical power of the study. Additionally, although the KDQOL-36 is a validated and widely used instrument, it relies on self-reported data, which may be subject to bias and individual perception variability. Furthermore, certain potentially relevant factors, such as socioeconomic status, educational level, and detailed treatment adherence, were not systematically assessed and may have influenced HRQoL outcomes. Despite these limitations, the study provides valuable insights into the multidimensional determinants of quality of life in patients with diabetic nephropathy.

CONCLUSIONS

Health-related quality of life is significantly impaired in patients with diabetic nephropathy and is influenced by a complex interplay of clinical, laboratory, and demographic factors. Advanced CKD stages, dialysis, comorbidities, and poor metabolic control emerged as key determinants of reduced HRQoL. These findings highlight the importance of a comprehensive, patient-centered approach that extends beyond traditional clinical management to include optimization of metabolic control, correction of anemia and nutritional deficits, and targeted interventions aimed at reducing the burden of disease and improving overall well-being.

Overall, our results confirm that HRQoL in patients with diabetic nephropathy is multifactorial, reflecting not only disease severity but also the cumulative effects of comorbidities, treatment burden, and systemic complications. These findings emphasize the need for a comprehensive, patient-centered approach that integrates optimal metabolic control, management of anemia and inflammation, and strategies aimed at reducing the burden of renal replacement therapy.

Conflict of interest: Nothing to declare

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ORIGINAL ARTICLE

OTOACUSTIC EMISSION MEASUREMENTS IN COMPARISON TO AUDIOMETRY FOR THE FOLLOW-UP OF HEARING IN HEMODIALYSED PATIENTS

Evis Bendo[1], Nirian Bendo[2]

[1]ENT Department, University Hospital Center "Mother Teresa", Tirana, Albania

[2]Neurosurgery Department, Trauma Hospital, Tirana, Albania

Corresponding E-mail: drbendo@gmail.com

ABSTRACT

Introduction. Patients undergoing hemodialysis frequently exhibit some degree of sensorineural hearing loss (SNHL). The underlying mechanisms are not fully understood, and it remains uncertain whether this impairment results from the hemodialysis procedure itself or from chronic renal failure (CRF).

Methods. A total of 61 patients (122 ears) were examined: 39 subjects undergoing hemodialysis treatment for more than one year, 12 subjects initiating hemodialysis, and 10 healthy controls. Hearing assessment was performed using pure tone audiometry (PTA) and distortion product otoacoustic emissions (DPOAE). DPOAE was applied only in participants with normal middle ear conditions and hearing thresholds better than 30 dB HL, using a 65/55 dB SPL (L1/L2) setting. Additional clinical parameters, including blood pressure, body weight, and blood chemistry, were also recorded.

Results. Both PTA and DPOAE results demonstrated poorer hearing thresholds in patients with chronic renal failure compared to controls, particularly at high frequencies. However, there was no significant difference in hearing outcomes between patients undergoing long-term hemodialysis and those who had recently initiated treatment.

Conclusion. Sensorineural hearing loss in patients with chronic renal failure appears to be associated with the underlying renal disease itself rather than the hemodialysis treatment procedure. Careful monitoring of hearing in CRF patients is recommended as part of their long-term management.

Keywords. Sensorineural hearing loss; Chronic renal failure; Hemodialysis; Pure tone audiometry; Distortion product otoacoustic emissions.

OTOEMISIONET AKUSTIKE KUNDREJT AUDIOMETRISË PËR MONITORIMIN E DËGJIMIT TEK PACIENTET NËN HEMODIALIZË

ABSTRAKT

Hyrje. Pacientët me insuficiencë renale kronike që i nënshtrohen hemodializës shpesh paraqesin çrregullime të ndryshme sistemike, përfshirë edhe ulje të dëgjimit. Studimet sugjerojnë se ndryshimet metabolike, çrregullimet elektrolitike dhe faktorë të tjerë të lidhur

me sëmundjen renale mund të ndikojnë në funksionin koklear. Qëllimi i këtij studimi ishte të vlerësojë funksionin e dëgjimit tek pacientët me insuficiencë renale kronike dhe të analizojë ndikimin e hemodializës në dëgjim.
Metodologjia. Në studim u përfshinë 61 pacientë (122 veshë). Prej tyre, 39 ishin pacientë që i nënshtroheshin dializës për më shumë se 1 vit, 12 ishin pacientë që sapo kishin filluar dializën, ndërsa 10 pacientë shërbyen si grup kontrolli. Vlerësimi i dëgjimit u krye me audiometri tonale të pastër dhe me otoemisione akustike të tipit Distortion Product (DPOAE), vetëm tek pacientët me funksion normal të veshit të mesëm. Për testimin DPOAE u përdorën nivele stimuluese 65/55 dB SPL (L1/L2). Gjithashtu u analizuan parametra të tjerë klinikë dhe laboratorikë, përfshirë tensionin arterial, analizat biokimike, nivelin e elektroliteve dhe urinën komplet.
Rezultate. Rezultatet e audiometrisë dhe testimeve DPOAE treguan një dëgjim më të dobët tek pacientët me insuficiencë renale kronike krahasuar me grupin e kontrollit. Ulja e dëgjimit ishte më e theksuar në frekuencat e larta.
Megjithatë, nuk u evidencua një ndikim i drejtpërdrejtë i hemodializës në përkeqësimin e dëgjimit, pasi nuk u vërejtën ndryshime domethënëse midis pacientëve që sapo kishin filluar dializën dhe atyre me kohëzgjatje më të gjatë trajtimi.
Përfundime. Ulja e dëgjimit tek pacientët me insuficiencë renale kronike është kryesisht e tipit neurosensorial dhe më e theksuar në frekuencat e larta. Hemodializa nuk rezultoi të ketë ndikim të drejtpërdrejtë në dëgjim. Prandaj, çrregullimet e dëgjimit duket se janë pasojë e vetë sëmundjes renale kronike dhe jo e trajtimit me hemodializë.
Fjale kyç: ulje neurosensoriale degjimi, insuficence renale kronike, audiometri e toneve te pastra, otoemisione akustike.

INTRODUCTION

There are many anatomical, physiological, pharmacological, and pathological similarities between the nephrons and the stria vascularis of the cochlea, and hearing loss has been reported in patients with renal failure (1,2).

The gross anatomy of the kidney and cochlea differ greatly, although there are many similarities at the ultrastructural level. Both contain epithelial structures in close contact with their vascular supply. The basement membrane lies closely opposed to the capillary endothelium in both Bowman's capsule and the proximal renal tubule of the kidney, and around the capillaries of the stria vascularis. They may also share common antigenicity (3,4). These similarities may account for the parallel effects of medications (i.e., the nephrotoxic and ototoxic effects of aminoglycosides) and immunological factors on the two organs.

Inner ear and kidney development are influenced by similar genetic factors in hereditary conditions such as Alport's syndrome and branchio-oto-renal syndrome.

Recording OAEs implies a functioning cochlea and a healthy middle ear mechanism. Distortion product otoacoustic emissions (DPOAE) are produced when the ear is stimulated with a combination of pure tones that are close in frequency (the primary tones). DPOAEs

reflect non-linear processes of hair cell motion and are generated by the active cochlear mechanisms responsible for enhancing basilar membrane vibration, the 'cochlear amplifier.'

The incidence of sensorineural hearing loss (SNHL) among patients with chronic renal failure (CRF) is considerably higher than in the general population. Bazzi et al. (5) found an incidence of 77%, including patients with mild and very mild hearing loss. Ozturan and Lam (6) reported moderate to severe hearing loss in 46% of tested patients. The consensus in audiometric findings among CRF patients indicates high-frequency hearing loss (7,8), often with a notch at 6 kHz (6).

The presence of hearing loss and estimation of type and degree constitute common methods used to investigate the effects of renal disease on the auditory system. In addition to audiometry and tympanometry, otoacoustic emissions (OAEs), particularly distortion product otoacoustic emissions (DPOAEs), are used to evaluate cochlear function.

MATERIALS AND METHODS

A total of 61 participants (122 ears) were included in the study. Among them, 39 patients had been undergoing hemodialysis for more than one year, 12 patients were newly initiated on hemodialysis, and 10 age-matched healthy individuals served as controls. Inclusion criteria for patients were aged between 15 and 50 years, documented hearing impairment following the onset of renal failure, no history of significant noise exposure, no history of diabetes mellitus, and no previous renal transplantation. Healthy volunteers met the following criteria: age 15-50 years, normal renal function tests, and no history of noise exposure, diabetes, or renal transplantation. Renal failure was diagnosed based on elevated blood urea and serum creatinine levels in association with oliguria. Written informed consent was obtained from all participants. Audiological assessment included tympanometry and pure-tone audiometry. Distortion Product Otoacoustic Emissions (DPOAE) testing was performed only in subjects with normal middle ear function and hearing thresholds better than 30 dB HL. DPOAE measurements were conducted using primary tones set at L1/L2 levels of 65/55 dB SPL. Additional clinical parameters, including blood pressure, body weight, and blood chemistry values, were also recorded and analyzed.

OBSERVATIONS

In the CRF patients' group, among the patients newly initiated on hemodialysis, there were 5 out of 12 patients with SNHL, especially in high frequencies, and in the group with the patients undergoing hemodialysis for more than one year, there were 24 patients out of 39 with SNHL. All 29 patients of CRF with SNHL had a moderately severe to severe degree of hearing loss. As the number of hemodialysis patients increases, the chances of developing SNHL and the degree also increase. There is a high incidence of SNHL even in patients with long-standing CRF. As the duration of CRF progresses, patients become more prone to develop hearing loss.

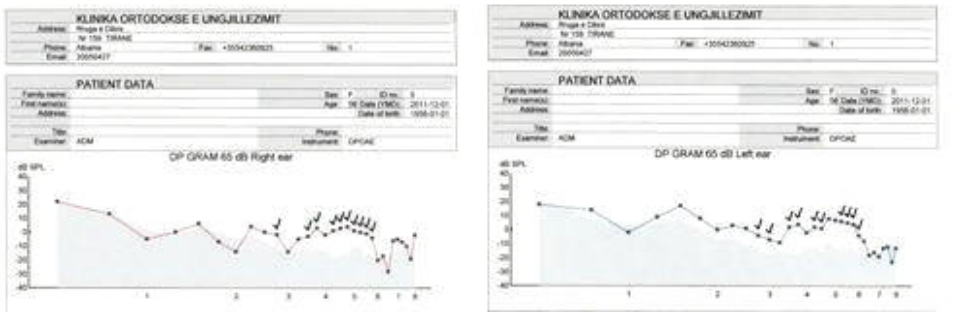
DPOAE raised the percentages of detection of SNHL, indicating that it is a better technique than the conventional pure-tone audiometry for the evaluation of hearing acuity. In the study

of the control group of 10 healthy volunteers (selected from patients of ENT emergency visited for different problems other than ear problems) only 1 case had SNHL, which was moderate and of high frequency range. All the healthy volunteers had serum creatinine, blood urea, serum electrolyte levels within normal limits, and their systolic blood pressure <140 mmHg.

Patients with SNHL over 70 dB had significantly low sodium and higher potassium and chloride values. This shows the role of electrolytes in causing SNHL. Serum creatinine indicates the extent of renal disease, but its levels are raised in all cases of CRF with or without SNHL.



Figure 1. Normal values in both DPOAE and Audiometry



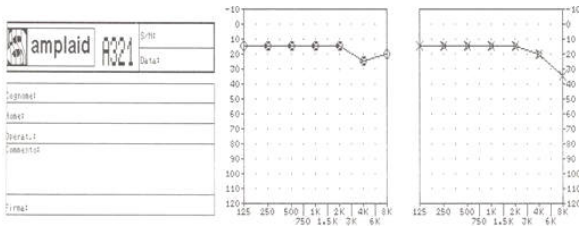


Figure 2. Detection of hearing loss in DPOAE but not in Audiometry.

DISCUSSION

Distortion product otoacoustic emissions (DPOAEs) are sounds emitted in response to two simultaneous tones of different frequencies. A setting of 65/55 dB SPL (L1/L2) is typically used. DPOAEs reflect nonlinear processes of outer hair cell motion and are generated by the active cochlear mechanisms responsible for enhancing basilar membrane vibration ("cochlear amplifier").

Since the cochlea and kidney may share antigenicity (3,4) and employ similar mechanisms of active transport of fluids and electrolytes, mediated by the stria vascularis and glomerulus, respectively (6,9), this may explain the similar influence of genetic factors and medications on both organs.

The etiological factors linked to hearing loss in renal failure include the use of ototoxic medications, electrolyte disturbances (10), hypertension (11,12), and hemodialysis treatment itself (5,13,14). Brookes (15) suggested that vitamin D deficiency might be a contributing factor to hearing loss in renal failure. Albertazzi et al. (16) documented alterations in the peripheral and central nervous system in uremic patients, demonstrating the existence of "uremic neuropathy."

Renal failure is linked to hearing loss irrespective of treatment modality; however, it remains difficult to separate the effects of disease duration, hemodialysis treatment, medication ototoxicity, age, noise exposure, and their possible interactions.

As treatments become more efficient and patients' life spans increase, there is a better chance of observing co-existing conditions, as well as the added factors of geriatric concerns.

Treatment evolution may have modified the contribution of several factors in causing hearing loss. For example, hyponatremia was common in earlier decades (10), but is less frequent with modern hemodialysis techniques.

From these observations, the positive factor that may be a cause of hearing loss in CRF patients was the long duration of the renal failure. The hearing loss in these patients is not of genetic origin; it happens even after exclusion of known risk factors such as noise exposure, ototoxic drugs, head injuries, old age, etc. The presence of additional factors accelerates the cause of hearing loss. The presence of electrolyte imbalance, hypertension, proteinuria, and hemodialysis is one of the factors that seem to have a cumulative effect on the deterioration of hearing in patients who were suffering from CRF.

CONCLUSION

Patients with long-standing chronic renal failure are at increased risk of developing bilateral, symmetrical high-frequency sensorineural hearing loss. The severity of hearing loss may be influenced by the duration of chronic renal failure and cumulative metabolic disturbances. Electrolyte imbalance and uncontrolled hypertension further contribute to the development and severity of SNHL, whereas elevated serum creatinine and blood urea levels alone are not reliable predictors of hearing loss.

As survival in CRF patients improves, hearing impairment is becoming increasingly prevalent and clinically relevant in this population. DPOAE testing demonstrated higher sensitivity in detecting SNHL compared to conventional pure-tone audiometry, supporting its value as a useful tool for early auditory assessment in patients with chronic renal failure.

Conflict of interests. The author declares no conflict of interest.

Author contribution. All authors contributed to the preparation of the manuscript and approved the final version.

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REVIEW ARTICLE

IMMUNOGENETIC FACTORS IN AUTOIMMUNE THYROID DISEASES: CENTRAL ROLE OF HLA IN DISEASE SUSCEPTIBILITY

Megi Lekbello[1], Dorina Ylli[2], Marjeta Kërmaj[1], Violeta Hoxha[2], Klodiana Poshi[2]

[1]University Hospital Center "Mother Teresa", Tirana, Albania
[2]University of Medicine, Tirana, Albania

Corresponding E-mail: dorina.ylli@umed.edu.al

ABSTRACT

Autoimmune thyroid diseases (AITDs), including Graves' disease (GD) and Hashimoto's thyroiditis (HT), represent the most common organ-specific autoimmune disorders worldwide. Their development results from a complex interaction between genetic susceptibility and environmental triggers. Among genetic determinants, human leukocyte antigen (HLA) genes located within the major histocompatibility complex (MHC) are of primary importance. Specific HLA class II polymorphisms influence antigen presentation, T-cell activation, and tolerance breakdown. This article reviews the immunogenetic basis of AITD with emphasis on HLA structure, functional polymorphisms, molecular mechanisms of susceptibility, and available population data, highlighting the need for further investigation in the Albanian population.

Keywords: HLA, thyroid, genetics, Hashimoto, Graves.

FAKTORËT IMUNOGJENETIKË NË SËMUNDJET AUTOIMUNE TË GJËNDRËS TIROIDE: ROLI KYÇ I HLA NË NDJESHMËRINË NDAJ SËMUNDJES

ABSTRAKT

Sëmundjet autoimune të tiroides (AITD), përfshirë sëmundjen e Graves (GD) dhe tiroiditin Hashimoto (HT), përfaqësojnë çrregullimet autoimune organ specifike më të shpeshta në nivel global. Zhvillimi i tyre është rezultat i një ndërveprimi kompleks ndërmjet predispozitës gjenetike dhe faktorëve mjedisorë nxitës. Ndër determinantët gjenetikë, gjenet e antigjenit leukocitar human (HLA), të lokalizuara në kompleksin kryesor të histokompatibilitetit (MHC), kanë rëndësi parësore. Polimorfizmat specifike të HLA të klasës II ndikojnë në prezantimin e antigjeneve, aktivizimin e qelizave T dhe prishjen e mekanizmave të tolerancës imune. Ky artikull rishikon bazën imunogjenetike të AITD, me theks në strukturën e HLA, polimorfizmat funksionale, mekanizmat molekularë të ndjeshmërisë ndaj sëmundjes dhe të dhënat e disponueshme në popullata të ndryshme, duke theksuar nevojën për studime në popullatën shqiptare.

Fjalë kyçe: HLA, tiroide, gjenetikë, tiroiditi i Hashimotos, sëmundja e Graves.

INTRODUCTION

Autoimmune thyroid diseases affect approximately 2–5% of the general population, with a significantly higher prevalence among women, ranging from 5–15% (1). The two principal clinical entities are Graves' disease (GD), characterized by hyperthyroidism due to stimulating autoantibodies against the thyroid-stimulating hormone receptor (TSHR), and Hashimoto's thyroiditis (HT), characterized by progressive autoimmune destruction of thyroid tissue leading to hypothyroidism.

Although GD and HT manifest with opposing thyroid functional states, they share fundamental immunopathological mechanisms. Both diseases involve lymphocytic infiltration of the thyroid gland, breakdown of immune tolerance, and production of thyroid-specific autoantibodies such as anti-thyroglobulin (TgAb), anti-thyroid peroxidase (TPOAb), and, in GD, anti-TSHR antibodies (2,3). These shared mechanisms suggest overlapping genetic predispositions with disease-specific modifiers.

This article represents a narrative review focused on the immunogenetic mechanisms involved in autoimmune thyroid diseases, with particular emphasis on HLA-related susceptibility. Literature was selected through a non-systematic search of PubMed, Scopus, and Google Scholar databases using keywords including "autoimmune thyroid disease", "Hashimoto thyroiditis", "Graves disease", "HLA", "MHC", and "immunogenetics". Priority was given to original studies, review articles, and landmark publications addressing HLA associations and molecular mechanisms of disease susceptibility.

Genetic Contribution to Autoimmune Thyroid Diseases

The role of genetic predisposition in AITD has been strongly supported by familial aggregation studies. Approximately 33% of siblings of patients with GD or HT develop AITD, and up to 56% of siblings produce thyroid autoantibodies (4). Such findings indicate that genetic susceptibility extends beyond overt clinical disease to subclinical autoimmunity.

Twin studies provide further compelling evidence. Concordance rates are significantly higher in monozygotic (MZ) twins compared with dizygotic (DZ) twins. For GD, concordance reaches approximately 35% in MZ twins versus 3% in DZ twins. For HT, concordance has been reported at 55% in MZ twins and nearly 0% in DZ twins (4). These data clearly demonstrate a strong heritable component, while incomplete concordance underscores the contribution of environmental triggers.

Multiple susceptibility genes have been implicated in AITD, including immune regulatory genes (e.g., CTLA-4, PTPN22, CD40) and thyroid-specific genes (e.g., thyroglobulin). However, among all genetic factors, the HLA region remains the most consistently associated locus.

The Major Histocompatibility Complex (MHC)

The major histocompatibility complex (MHC) is located on the short arm of chromosome 6 (6p21) (5). It is the most gene-dense and polymorphic region of the human genome and is divided into three functional subregions: class I, class II, and class III (6).

Class I MHC Molecules

HLA class I molecules consist of an α (heavy) chain associated with β2-microglobulin. The heavy chain contains two peptide-binding domains (α1 and α2), an immunoglobulin-like domain (α3), a transmembrane segment, and a cytoplasmic tail. It is encoded by the HLA-A, HLA-B, and HLA-C loci.

Class I molecules present endogenous peptides to CD8+ cytotoxic T lymphocytes, which eliminate infected or abnormal cells. Non-classical class I molecules include HLA-E, -F, and -G, as well as pseudogenes (5,7).

Class II MHC Molecules

Class II molecules are particularly relevant to autoimmune disease. They are normally expressed on professional antigen-presenting cells (APCs), including B cells, macrophages, dendritic cells, Langerhans cells, thymic epithelial cells, and activated T cells. They consist of α and β chains, each containing a peptide-binding domain, an immunoglobulin-like domain, and a transmembrane region.

These molecules are encoded by genes within the HLA-DP, HLA-DQ, and HLA-DR regions. CD4+ T helper cells recognize peptides presented by class II molecules and orchestrate adaptive immune responses (7).

Importantly, class II genes exhibit marked polymorphism, particularly within peptide-binding regions. Variability in amino acid composition directly affects peptide-binding specificity and stability, making these genes central determinants of autoimmune susceptibility.

Class III Region

The class III region encodes molecules involved in inflammatory responses, including complement components (C2, C4, factor B), tumor necrosis factor-α (TNF-α), lymphotoxin, and several heat-shock proteins (7). Although not directly involved in antigen presentation, these molecules contribute to immune regulation and inflammation.

HLA and Susceptibility to Autoimmune Thyroid Disease

Because the HLA region contains numerous immune response genes and exhibits high polymorphism, it was the first candidate region investigated in AITD.

T cells recognize antigenic peptides only when presented by specific HLA molecules (8). Different HLA alleles bind distinct peptide repertoires with varying affinities. If an HLA molecule efficiently binds a thyroid autoantigen, it may present it to autoreactive T cells that have escaped central or peripheral tolerance (5,9). This interaction represents a critical step in the initiation of autoimmune thyroid disease.

HLA Associations in Graves' Disease

In Caucasian populations, susceptibility to GD is strongly associated with HLA-DR3 and the linked allele HLA-DQA1*0501 (10–12). Further molecular analysis identified arginine at position 74 (Arg74) in the HLA-DRβ1 chain as a key determinant (13).

Position 74 lies within pocket 4 (P4) of the peptide-binding groove. Replacement of a neutral amino acid (alanine or glutamine) with positively charged arginine alters the three-dimensional configuration of the binding pocket. Structural modeling studies demonstrate

that this substitution modifies peptide-binding characteristics and influences T-cell activation (13).
Functional studies have shown that HLA-DR3 preferentially binds immunodominant peptides derived from the TSH receptor. Additionally, interaction between DRβ1-Arg74 and a thyroglobulin gene variant confers an odds ratio exceeding 16, suggesting synergistic genetic and biochemical interactions during disease initiation (14).

HLA Associations in Hashimoto's Thyroiditis
In HT, susceptibility has been associated with HLA-DR3, HLA-DR5, HLA-DR4, and HLA-DQw7 (DQB1*0301) (15–17). Although overlap exists between GD and HT, the strength and pattern of associations differ, indicating partially distinct immunogenetic mechanisms.

Evidence from Type 1 diabetes mellitus
Insights into structural-functional mechanisms of HLA susceptibility are well illustrated by Type 1 diabetes mellitus. In this disease, aspartic acid at position 57 of the HLA-DQ β-chain plays a pivotal role (18–20).
Absence of Asp57 alters the charge and structure of the peptide-binding groove, allowing insulin peptides to bind more effectively and be presented to autoreactive T cells. Presence of Asp57, in contrast, stabilizes the groove and reduces pathogenic peptide binding (19,20). This example demonstrates how a single amino acid substitution can significantly influence autoimmune risk.
A similar structural principle likely applies to HLA-DRβ1 Arg74 in GD.

Intrathyroidal Antigen Presentation and Local Immune Activation
For thyroid autoimmunity to develop, autoantigens must be presented locally within the thyroid gland or its draining lymph nodes. In GD and HT, thyroid epithelial cells (thyrocytes) aberrantly express HLA class II molecules (21).
This abnormal expression enables thyrocytes to function as facultative APCs, directly presenting thyroid autoantigens to CD4+ T cells. However, effective T-cell activation requires both antigen presentation and co-stimulatory signaling. CD40 expression on thyrocytes may provide this additional signal, contributing to sustained immune activation and disease progression (22).
Thus, autoimmune thyroid disease likely results from the convergence of genetic susceptibility, structural HLA determinants, local antigen presentation, and co-stimulatory signaling.

HLA Distribution in the Albanian Population
Data regarding HLA allele distribution in the Albanian population remain limited, despite the recognized importance of HLA polymorphisms in autoimmune diseases. In 2009, Sulcebe et al. analyzed HLA allele and haplotype frequencies in 160 healthy unrelated Albanian individuals and demonstrated that the Albanian population shares several immunogenetic characteristics with other southeastern European populations, while also presenting specific haplotypic patterns (17).

The most frequent HLA-A-B-DRB1 haplotypes identified included A02-B18-DRB111, A02-B51-DRB116, and A01-B08-DRB103. Some of these haplotypes contain alleles previously implicated in susceptibility to autoimmune conditions, including autoimmune thyroid diseases in other ethnic groups. However, no studies to date have specifically investigated the relationship between HLA polymorphisms and Graves' disease or Hashimoto's thyroiditis in Albanian patients.

The six most frequent HLA-A-B-DRB1 haplotypes were:

- A02-B18-DRB111 (5.60%)
- A02-B51-DRB116 (4.74%)
- A01-B08-DRB103 (3.48%)
- A24-B35-DRB111 (2.77%)
- A02-B51-DRB113 (2.21%)
- A24-B35-DRB114 (1.89%)

This lack of national data represents an important gap in the current understanding of autoimmune thyroid disease susceptibility within the Albanian population. Since HLA associations often vary significantly among ethnic and geographic populations, findings derived from Caucasian, Asian, or other European cohorts cannot necessarily be extrapolated directly to Albanian individuals. Population-specific immunogenetic studies are therefore essential to determine whether known susceptibility alleles such as HLA-DR3, HLA-DR5, DQA1*0501, or specific amino acid polymorphisms including DRβ1-Arg74 are similarly associated with disease risk in Albania.

Furthermore, characterization of HLA profiles in Albanian patients with autoimmune thyroid diseases could contribute to improved understanding of disease heterogeneity, familial clustering, antibody production, and potentially different clinical phenotypes. Such studies may also provide the basis for future personalized approaches in risk stratification, early diagnosis, and targeted immunological monitoring.

Given the increasing prevalence of autoimmune diseases and the current absence of local immunogenetic data, further multicenter studies involving Albanian patients with Graves' disease and Hashimoto's thyroiditis are strongly warranted.

CONCLUSION

Autoimmune thyroid diseases arise from complex interactions between genetic predisposition and environmental factors. Among genetic determinants, HLA class II polymorphisms play a central role by regulating antigen presentation and T-cell activation. Specific amino acid substitutions within the peptide-binding groove can alter peptide affinity and influence autoimmune risk.

Understanding these immunogenetic mechanisms in diverse populations, including Albania, may provide valuable insights into disease susceptibility, pathogenesis, and potential strategies for personalized risk assessment and early intervention.

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REVIEW ARTICLE

PHYSIOPATHOLOGICAL MECHANISMS OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE DISEASES

Anxhela Qirko (Gurakuqi) [1], Taulant Gishto [2]
[1]Head of the Department of Physiopathology, Faculty of Medicine, UMT, Tirana
Allergy Specialist, Service of Allergology and Clinical Immunology, UHC, Tirana
[2]Lecturer at the Department of Physiopathology, Faculty of Medicine, UMT, Tirana
Cardiology Specialist, Service of Cardiology, UHC, Tirana
Corresponding E-mail: anxhela_g@yahoo.com

ABSTRACT

This article summarizes the main pathophysiological mechanisms that link chronic obstructive pulmonary diseases, especially COPD and emphysema, to the development of pulmonary hypertension (PH). Unlike bronchial asthma, COPD and emphysema are characterized by irreversible obstruction, mainly associated with structural changes in the bronchial wall and destruction of the alveolar architecture, mainly caused by smoking. In COPD, mucus hyperproduction, hypertrophy of mucous glands, and decreased mucociliary clearance follow persistent airway narrowing, while in emphysema, damage to elastic fibers due to protease–antiprotease imbalance predominates, resulting in bronchiolar collapse and "air trapping".

These structural changes also progressively affect the pulmonary vascular bed, leading to the installation of PH through several interconnected mechanisms. Alveolar hypoxia causes hypoxic vasoconstriction, a compensatory mechanism that diverts blood flow to more ventilated areas, but which chronically increases vascular resistance. Chronic inflammation induced by smoking favors a profile of vasoconstrictor mediators and impairs endothelial function. Vascular remodeling, mediated by factors such as TGF-β, contributes to vascular wall stiffening and thickening, making the process irreversible.

Other factors include polycythemia in response to hypoxia, vasoconstrictive acidosis, pulmonary thromboses that worsen the ventilation/perfusion ratio, and the reduction of the capillary network in emphysema, which reduces the surface area for gas exchange. Pulmonary hyperinflation and increased intrathoracic pressures negatively affect venous return and cardiac output, activating the sympathetic system and the renin–angiotensin–aldosterone system, which further potentiate pulmonary vasoconstriction.

In **conclusion**, PH in the context of COPD and emphysema is the result of a complex interaction between hypoxia, inflammation, vascular remodeling, and hemodynamic factors, representing an important prognostic and therapeutic complication.

Key words: Chronic obstructive diseases, COPD, emphysema, pulmonary hypertension, PH

MEKANIZMAT FIZIOPATOLOGJIKË TË HIPERTENSIONIT PULMONAR, NË PACIENTË ME PATOLOGJI OBSTRUKTIVE KRONIKE

ABSTRAKT

Ky artikull përmbledh mekanizmat kryesorë fiziopatologjikë që lidhin patologjitë obstruktive kronike pulmonare, veçanërisht SPOK-un dhe emfizemën, me zhvillimin e hipertensionit pulmonar (HTP). Ndryshe nga astma bronkiale, SPOK-u dhe emfizema karakterizohen nga obstruksion jo i kthyeshëm, i lidhur kryesisht me ndryshime strukturore të murit bronkial dhe shkatërrimin e arkitekturës alveolare, të shkaktuara kryesisht nga duhani. Në SPOK, hiperprodhimi i mukusit, hipertrofia e gjëndrave mukoze dhe ulja e klirensit mukociliar çojnë në ngushtim të qëndrueshëm të rrugëve ajrore, ndërsa në emfizemë dominon dëmtimi i fibrave elastike për shkak të çekuilibrit proteazë–antiproteazë, me pasojë kolaps bronkiolar dhe "air trapping".

Këto ndryshime strukturore ndikojnë progresivisht edhe në shtratin vaskular pulmonar, duke çuar në instalimin e HTP përmes disa mekanizmave të ndërthurur. Hipoksia alveolare shkakton vazokonstriksion hipoksik, një mekanizëm kompensator që devijon rrjedhën e gjakut drejt zonave më të ventiluara, por që në mënyrë kronike rrit rezistencën vaskulare. Inflamacioni kronik i nxitur nga duhani favorizon një profil mediatorësh vazokonstriktorë dhe dëmton funksionin endotelial. Rimodelimi vaskular, i ndërmjetësuar nga faktorë si TGF-β, kontribuon në ngurtësimin dhe trashjen e murit vaskular, duke e bërë procesin të parikthyeshëm.

Faktorë të tjerë përfshijnë policiteminë si përgjigje ndaj hipoksisë, acidozën me efekt vazokonstriktor, trombozat pulmonare që përkeqësojnë raportin ventilim/perfuzion, si dhe reduktimin e rrjetit kapilar në emfizemë, që ul sipërfaqen e shkëmbimit të gazeve. Hiperinflacioni pulmonar dhe rritja e presioneve intratorakale ndikojnë negativisht në kthimin venoz dhe debitin kardiak, duke aktivizuar sistemin simpatik dhe sistemin reninë–angiotenzinë–aldosteron, të cilët përforcojnë më tej vazokonstriksionin pulmonar.

Në përfundim, HTP në kontekstin e SPOK dhe emfizemës është rezultat i një ndërveprimi kompleks midis hipoksisë, inflamacionit, rimodelimit vaskular dhe faktorëve hemodinamikë, duke përfaqësuar një komplikacion të rëndësishëm prognostik dhe terapeutik.

Fjalë kyçe: Sëmundje obstructive kronike, SPOK, emfizemë, hypertension pulmonar, HTP

INTRODUCTION

Chronic obstructive pulmonary diseases, including bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), and emphysema, represent a major challenge for global public health. These conditions are characterized not only by structural and functional changes in the bronchial tree - such as increased airway resistance - but also by a progressive and often irreversible damage to the pulmonary vascular bed. While in bronchial asthma, vascular changes may be more limited and often associated with TH2-type inflammation, in COPD and emphysema, vascular alterations predominate over the course of the disease (1).

The statistics are alarming: by 2030, COPD is predicted to be the fourth leading cause of death globally. The main etiology remains smoking, which triggers a cascade of reactions ranging from mucus hyperproduction to parenchymal destruction. In COPD, the obstruction is largely irreversible due to bronchial wall thickening (Reid index increase above 0.7) and mucous gland hypertrophy. On the other hand, emphysema represents the most aggressive form of structural destruction, where the loss of peri-bronchial and peri-alveolar elastic fibers leads to the collapse of small airways and the formation of areas of "air trapping".
Pulmonary Hypertension (PH) in these patients is a serious complication that determines survival (2). According to the latest ECS/ERS 2022 guidelines, PH is diagnosed when the Mean Pulmonary Artery Pressure (mPAP), measured by cardiac catheterization, exceeds 20 mmHg. This transition from a purely respiratory disease to a condition with severe hemodynamic implications occurs through a series of complex pathophysiological mechanisms that will be analyzed below.

DETAILED ANALYSIS OF PATHOPHYSIOLOGICAL MECHANISMS
Below are listed and elaborated on 9 mechanisms that lead to the installation and progression of PTH in the setting of chronic obstruction:

1. Alveolar Hypoxia and Hypoxic Pulmonary Vasoconstriction (HPV): This is the earliest and most critical mechanism (3). The pulmonary vascular bed possesses a unique property: unlike the systemic circulation (where hypoxia induces vasodilation), in the lungs, it causes vasoconstriction of pre-capillary arterioles. This process is known as the Euler-Liljestrand Reflex. The physiological purpose is protective: to divert blood from poorly ventilated alveoli to those with high oxygen levels, attempting to maintain the ventilation/perfusion (V/Q) ratio and minimize the “shunt effect.” However, when hypoxia becomes chronic and widespread (as in COPD), this vasoconstriction becomes ubiquitous, dramatically increasing pulmonary vascular resistance and serving as a cornerstone for PH.

2. Chronic Inflammation and Humoral Mediators: Tobacco and other irritants induce a chronic inflammatory state in the airways and blood vessels (4). This inflammation is characterized by increased chemotaxis of neutrophils, which are the main source of elastase. At the endothelial level, this inflammation causes an imbalance between vasoactive substances. There is an increase in the production of Endothelin-1 (a potent vasoconstrictor) and the activity of the enzyme ACE, while the availability of protective vasodilator substances such as Nitric Oxide (NO) and Prostacyclin decreases. This biochemical imbalance keeps the blood vessels in a state of constant high tone.

3. Vascular Remodeling and the Role of TGF-β: If vasoconstriction is a functional phenomenon, remodeling is the structural transformation that makes HTP irreversible (5). Under the influence of growth factors such as PDGFA, PDGFB, and especially TGF-β (Transforming Growth Factor beta), endothelial remodeling and dysfunction occur, as well as proliferation of smooth muscle cells in the arteriolar wall, together with an excessive deposition of extracellular matrix. This process damages the endothelium and "muscularizes" the normally thin vessels. Today, scientific attention has focused on drugs such as

Sotatercept, which act as a "trap" for TGF-β, aiming to block this signaling and potentially reverse vascular remodeling. Endothelial dysfunction is also directly provoked by smoking itself

4. Secondary Polycythemia and Blood Viscosity: Because of chronic hypoxia, the kidneys stimulate the production of erythropoietin, which leads to an increase in the number of erythrocytes, provoking polycythemia (6). Although this is intended to increase the oxygen-carrying capacity, the hemodynamic consequence is an increase in blood viscosity. According to Poiseuille's law, increased viscosity directly increases resistance to flow, requiring more pressure from the right ventricle to move blood through the pulmonary circulation.

5. Action of Acidosis: In patients with COPD, the tendency for CO_2 to accumulate in the blood leads to acidosis from hypoventilation (7). Interestingly, the decrease in pH has a synergistic effect with hypoxia in promoting pulmonary vasoconstriction. Acidosis modifies ion channels in vascular smooth muscle cells, promoting calcium entry and contraction, which further increases the load on the pulmonary artery.

6. "In-situ" Thrombosis and Microembolism: The combination of endothelial damage with blood stasis due to increased viscosity creates a state of hypercoagulability (8). Local thrombi (in situ) can form in small pulmonary vessels. These thrombi not only physically block the blood circulation but also release mediators such as Thromboxane A2 (TXA2), an extremely potent vasoconstrictor, creating a vicious cycle of increased pulmonary arterial pressure (PAP). Another consequence of thrombosis is the further deterioration of the ventilation/perfusion (V/P) ratio. It is known that in the context of the underlying disease (COPD and emphysema), this ratio has almost always been abnormal.

7. Destruction of the Capillary Bed in Emphysema: This is a purely structural mechanism. The destruction of the alveolar walls in emphysema also brings with it the disappearance of the capillaries located in those walls (9). With the loss of the total surface area of the vascular bed, the same volume of blood must pass through fewer vessels, which automatically increases the perfusion pressure (similar to reducing the number of lanes on a highway).

8. Hyperinflation and Intrathoracic Pressure Changes: In emphysema, "air trapping" causes the lungs to be constantly inflated, in a state of hyperinflation. This increases the positive intrathoracic pressure, which impedes venous return to the heart (10). The subsequent decrease in cardiac output activates the sympathetic nervous system, which, through alpha-adrenergic receptors, promotes further pulmonary vascular vasoconstriction.

9. Activation of the Renin-Angiotensin-Aldosterone System (RAAS): When cardiac output falls due to high intrathoracic pressures and right ventricular failure, not only is the sympathetic system stimulated, but the RAAS also becomes active as a compensatory mechanism (11). Angiotensin II, the main product of this system, is, among other things, a potent vasoconstrictor that acts both in the systemic circulation and in the lungs. This activation of Angiotensin II accelerates the transformation of mild hypertension into a severe hemodynamic state.

DISCUSSION

The link between PH and Cor Pulmonale in contemporary literature

The link between Pulmonary Hypertension and Cor Pulmonale represents one of the most sensitive points of modern cardiology and pneumology. Cor Pulmonale is defined as hypertrophy and dilatation of the right ventricle (RV), as a consequence of lung diseases that cause PH (Fig.1).

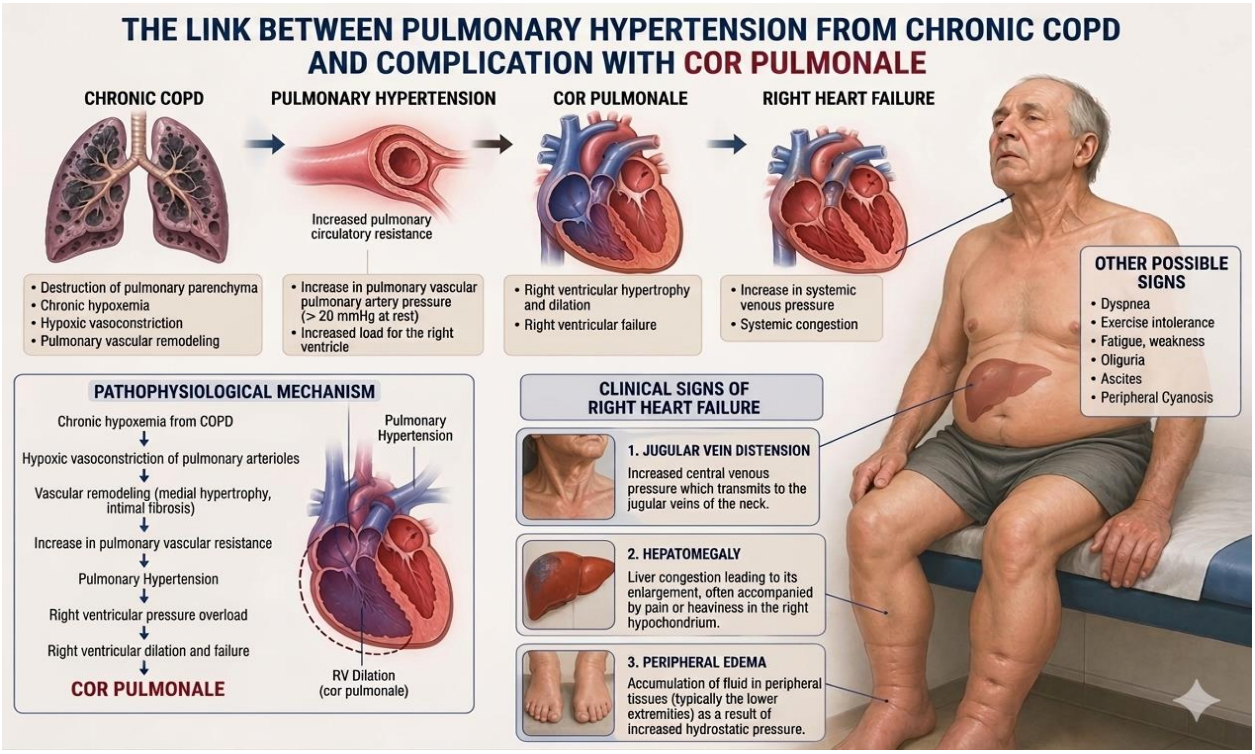


Figure 1. Pathophysiological link between chronic COPD-related pulmonary hypertension and Cor Pulmonale (Created by the authors based on literature data).

Analysis of Resistance and Adaptation: Contemporary literature, including studies by Gredic et al. (2020) and Sakao (2019), notes that the right ventricle is physiologically designed to work in a system with low pressure and high compliance. Unlike the left ventricle, the RV has a limited capacity to adapt to acute or chronic increases in "afterload" (opposing pressure). When mPAP exceeds the threshold of 20 mmHg, the VD begins to undergo initially adaptive changes (hypertrophy), which quickly turn into maladaptive (dilation and contractile failure).

Criticism of Traditional Treatments: One of the most critical aspects of the current literature is the failure of traditional pulmonary vasodilators (used for idiopathic PH) in patients with COPD and Cor Pulmonale. Studies show that drugs such as endothelin receptor antagonists or PDE5 inhibitors can be harmful in these patients, because by causing undifferentiated vasodilation, they "turn off" Hypoxic Pulmonary Vasoconstriction (HPV). This causes blood to go to unventilated areas, increasing the "shunt" and dramatically reducing oxygen saturation in peripheral blood.

The Emphysema Paradox: In the case of emphysema, the discussion becomes even more complex. Here, Cor Pulmonale is not only the result of pressure, but also of massive loss of the capillary bed and mechanical changes in the thorax. Recent literature suggests that the treatment of Cor Pulmonale in these patients should focus more on reducing lung volume (to reduce hyperinflation) and protecting the right ventricle through careful fluid management and diuretics, rather than aggressive vasodilators.

Prognostic Implications: The presence of Cor Pulmonale in the setting of COPD reduces the 5-year survival to less than 30%. A survival of 30% places Cor Pulmonale at a mortality level like many advanced forms of cancer, emphasizing the need for close monitoring and aggressive treatment of pathophysiological factors. This makes it necessary to identify early signs of RV failure through echocardiography and biomarkers such as NT-proBNP, long before the changes become irreversible.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the pathophysiology of PH in chronic obstructive disease is a multidimensional process, where genetic factors, exposure to tobacco, and failure of vascular regulatory mechanisms are combined. PH in COPD is not simply the result of oxygen deprivation, but of an interaction between chronic inflammation, vascular remodeling mediated by TGF-β, and parenchymal mechanical changes.
Some recommendations, after a critical analysis of the factors leading to PH, in the context of a chronic obstructive pathology, will be as follows:

- **Personalized Approach, as well as attention to Remodeling**: The future of therapy should shift from simple vasodilators towards "anti-remodeling" agents (such as Sotatercept) that aim to reverse the structural changes in blood vessels. The use of vasodilators should be done with the utmost care to avoid worsening the ventilation/perfusion ratio and severe hypoxemia.
- **RV Assessment**: Management of patients with chronic obstructive pathology should include regular monitoring of right ventricular function, as Cor Pulmonale remains the main factor dictating prognosis.
- **Prevention**: Smoking cessation remains the most effective intervention to stop the progression of inflammation and vascular remodeling before the installation of PH.

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REVIEW ARTICLE

RECENT DEVELOPMENTS IN HFpEF AND ATRIAL FIBRILLATION

Somida Kuka, Eneida Hoxha, Margarita (Gjata) Resuli

Department of Internal Medicine, UHC :Mother Teresa“ Tirana, Albania.

Corresponding E-mail: somida.kuka@gmail.com

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) often coexist and exacerbate each other through left atrial remodeling, increased filling pressures, inflammation, obesity, renal dysfunction, endothelial dysfunction, and impaired exercise tolerance. Recent data have shifted treatment from symptomatic therapy alone to phenotype-targeted therapy. Significant developments include the use of first-line sodium-glucose cotransporter-2 (SGLT2) inhibitors, recent validation of non-steroidal mineralocorticoid receptor antagonists, the utility of GLP-1/GIP-targeted weight-loss therapy for obesity-associated HFpEF, and increased proactive approaches to rhythm control in AF.

The effect of HFpEF on AF is bidirectional and clinically important. HFpEF leads to atrial fibrosis and raised filling pressures, while AF aggravates diastolic dysfunction via atrial contraction loss and irregular ventricular filling. Modern management thus depends on an integrated approach targeting congestion, metabolic failure, atrial disease, obesity, hypertension, diabetes mellitus, renal dysfunction and thromboembolic hazard.

This review provides an overview of recent pathophysiologic advances, diagnostic and treatment considerations, alongside recent and ongoing therapeutic developments for HFpEF followed by AF, including updates on the ESC guideline and large clinical trials.

Keywords: Heart failure; atrial fibrillation; preserved ejection fraction (HFpEF).

ZHVILLIMET E FUNDIT NË HFpEF DHE FIBRILACIONIN ATRIAL

ABSTRAKT

Hyrje. HFpEF dhe fibrilacioni atrial (FA) bashkëshoqërohen shpesh dhe përkeqësojnë njëri-tjetrin përmes rimodelimit atrial, inflamacionit dhe çrregullimeve metabolike. Zhvillimet e fundit përfshijnë përdorimin e inhibitorëve SGLT2, finerenonit, terapive GLP-1/GIP dhe strategjive më aktive të kontrollit të ritmit.HFpEF përfaqëson një nga format më të zakonshme të insuficiencës kardiake. FA është një komorbiditet shumë i shpeshtë dhe lidhet me simptoma më të rënda, hospitalizime të shpeshta dhe rrezik më të lartë tromboembolik. HFpEF shkakton dilatacion dhe fibrozë atriale, ndërsa FA përkeqëson funksionin diastolik dhe mbushjen ventrikulare.

Metoda. Ky review u realizua mbi bazën e literaturës së fundit shkencore dhe guideline-ve ESC. U analizuan studime të rëndësishme si EMPEROR-Preserved, DELIVER, FINEARTS-HF, STEP-HFpEF dhe EAST-AFNET 4. Fokus kryesor ishte diagnostika, terapia moderne dhe strategjitë e kontrollit të ritmit në pacientët me HFpEF dhe FA.
Resultate. Inhibitorët SGLT2 kanë treguar reduktim të hospitalizimeve dhe përmirësim të cilësisë së jetës në HFpEF. Finerenoni demonstroi reduktim të eventeve kardiovaskulare në pacientët me EF të ruajtur ose lehtësisht të reduktuar. Terapitë metabolike si semaglutide dhe tirzepatide përmirësuan simptomat dhe tolerancën fizike te pacientët obezë me HFpEF. Strategjitë e hershme të kontrollit të ritmit dhe ablacioni kateterik mund të përmirësojnë simptomat dhe kapacitetin funksional në pacientë të përzgjedhur.

Menaxhimi modern i HFpEF dhe FA po kalon drejt një qasjeje të personalizuar dhe multidisiplinare. Kontrolli i faktorëve të riskut si obeziteti, hipertensioni, diabeti dhe apnea e gjumit, mbetet esencial për suksesin afatgjatë terapeutik.

Përfundime. HFpEF dhe FA janë sindroma të ndërlidhura ngushtë. Terapitë moderne, veçanërisht SGLT2 inhibitorët dhe trajtimet metabolike, kanë ndryshuar ndjeshëm menaxhimin klinik. E ardhmja pritet të fokusohet në terapi të individualizuara sipas fenotipit të pacientit.

Fjalët kyce: insuficiencë kardiake, fibrilacion atrial, funksion i ruajtur.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) represents one of the fastest-growing cardiovascular syndromes in the world and accounts for over half of all heart failure cases globally. HFpEF does not consist of the same pathophysiologic mechanism as heart failure with reduced ejection fraction (HFrEF), and is due to impaired ventricular relaxation, increased ventricular stiffness, endothelial dysfunction, systemic inflammation, obesity, and multiple comorbidities. Atrial fibrillation (AF) is one of the most common and clinically significant comorbidities of HFpEF, and is highly prevalent in patients. Depending on the studied population, fibrillation in the HFpEF population accounts for about 40–60% of patients with AF. When HF happens simultaneously with both conditions, it is associated with increased mortality, recurrent heart-failure hospitalization, poor exercise capacity, decreased exercise ability, and increased thromboembolic risk (2). The relationship between AF and HFpEF is multifaceted and bidirectional. In HFpEF, elevated LV filling pressures cause left atrial enlargement, atrial fibrosis, and electrical remodeling and drive AF. In contrast, AF causes worsening diastolic filling due to loss of atrial contraction and shortened diastolic filling time, tachycardia-induced myocardial dysfunction, and increased neurohormonal activation (1,2). The therapeutic landscape of HFpEF has radically changed in the last few years. Treatments used to be mostly symptomatic and to control comorbidities. However, SGLT2 inhibitors are shown to lead to beneficial

effects in randomized clinical trials and may show further favorable effects with finerenone and obesity-targeted classes, including semaglutide and tirzepatide. At the same time, AF treatment has been moving toward integrated care strategies and earlier rhythm-control methodologies. The acknowledgment that AF might directly participate in the progression of HFpEF has sparked interest in catheter ablation and aggressive management of a subset of patients with increased risk factors (2). This review's objective is to review recent progress in the pathogenesis, diagnosis, management and treatment of HFpEF and AF along with the corresponding clinical significance.

MATERIAL AND METHODS

This review was performed as a narrative literature review with an emphasis on recent developments of heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF). A systematic search of the medical literature was conducted using PubMed, ESC guideline publications, and major peer-reviewed cardiovascular journals. The search encompassed studies published between 2020 and 2026, with a focus on randomized clinical trials, meta-analyses, and international guideline recommendations. The search terms used separately and together are as follows: “HFpEF,” “atrial fibrillation,” “SGLT2 inhibitors,” “empagliflozin,” “dapagliflozin,” “finerenone,” “GLP-1 agonists,” “tirzepatide,” “semaglutide,” “catheter ablation,” “rhythm control,” and “ESC Guidelines.” Priority was given to landmark studies and official guideline documents from the European Society of Cardiology (ESC). The major trials included EMPEROR-Preserved, DELIVER, FINEARTS-HF, STEP-HFpEF, SUMMIT, EAST-AFNET 4, and CABANA. Articles were selected based on their clinical applicability, methodological merits, and relevance to the management of current HFpEF and AF. Pathophysiology, diagnosis, pharmacotherapy, drug treatment, rhythm-control measures, obesity-associated HFpEF, and cardiovascular outcomes were targeted by data extraction.

The review was presented in themes that dealt with:

- Association of HFpEF and AF for disease progression;
- Novel pharmaceutical developments and developments in pharmaceutical therapy;
- Rhythm-control strategies;
- Diagnostic considerations;
- Phenotype-oriented management methods/protocols;
- Implications for practice.

As this is a narrative review of previously published studies, it did not require ethical committee approval or the consent of the patient.

RESULTS

Pathophysiological Interaction between HFpEF and AF

Recent reports found that HFpEF and AF are closely related disease processes, rather than separate clinical entities (3,4). High left ventricular filling pressures in HFpEF contribute to degenerative left atrial remodeling with dilation, fibrosis, endothelial dysfunction, and impaired reservoir function. Restructuring provides a proarrhythmogenic substrate that supports the genesis of AF.

The AF itself contributes to deteriorating HFpEF physiology due to:

- Atrial contractions collapse and ventricular filling impairment;
- Enhanced heart rate fluctuations;
- Cardiac output decreases during exertion;
- Myocardial damage due to tachycardia-driven heart failure;
- Neurohormonal activation;
- Increased pulmonary venous pressure.

The coexistence of HFpEF and AF correlates with reduced exercise tolerance; elevated levels of natriuretic peptide, increased hospitalization, and increased mortality. A growing number of studies have now suggested atrial cardiomyopathy as a main risk factor of HFpEF pathophysiology. Left atrial dysfunction may precede overt ventricular dysfunction, leading to symptomatology and disease progression (3,5).

SGLT2 Inhibitors

One of the most important changes in the management of HFpEF has been the implementation of SGLT2 inhibitors (6,7). The EMPEROR-Preserved trial showed that empagliflozin markedly reduced the combined endpoint of cardiovascular death and hospitalization due to heart failure in patients with HFpEF. Likewise, the DELIVER trial demonstrated good results with dapagliflozin in patients with mildly diminished or preserved ejection fraction. Notably, the most recent ESC guidelines recommend SGLT2 inhibitors across all categories of heart failure regardless of left ventricular ejection fraction. In patients with concomitant AF, SGLT2 inhibitors may also promote reduced atrial remodeling, inflammation, oxidative stress, and volume overload. Initial indications of potential antiarrhythmic action have been reported, but there is no randomized data specifically aimed at AF burden.

Clinical benefits of SGLT2 inhibitors include:

- Decreased heart-failure hospitalization;
- Symptom and quality of life benefits;
- Beneficial renal protection;
- Decrease of cardiovascular mortality;
- Common to HF phenotypes.

Finerenone and Mineralocorticoid Receptor Antagonism

Activation of mineralocorticoid receptors is associated with myocardial fibrosis, inflammation, vascular dysfunction, and renal dysfunction. Finerenone has been

shown to decrease worsening heart-failure events and cardiovascular death in patients with mildly reduced or preserved ejection fraction in the FINEARTS-HF trial. Finerenone may have a more selective receptor profile and lower rates of hyperkalemia and endocrine adverse events as compared with classical steroidal mineralocorticoid receptor antagonists (8). These findings provide support for a widening role of non-steroidal mineralocorticoid receptor antagonism for HFpEF patients, especially in patients with concomitant renal dysfunction and diabetes mellitus and with an increased inflammatory-metabolic load. However, continued surveillance of potassium concentration and renal function is key.

Obesity-Related HFpEF and Metabolic Therapy

Obesity-related HFpEF has become among the most clinically relevant HFpEF phenotypes (9,10). Obesity is associated with systemic inflammation, decreased ventricular compliance, and pulmonary hypertension, as well as endothelial dysfunction and epicardial adipose tissue build-up. AF is highly common in patients with obesity-related HFpEF. The STEP-HFpEF trial proved that semaglutide significantly improved symptoms, exercise capacity, quality of life, and body weight in obese HFpEF patients. Likewise, in the SUMMIT trial of tirzepatide, quality-of-life scores improved, and worsening heart-failure events declined. These results support the idea that targeted metabolic treatment can alter HFpEF progression significantly for certain phenotypes. Reducing weight also reduces blood pressure, decreases insulin resistance, severity of sleep apnea, alleviates inflammatory burden, and alters atrial remodeling, all of which can impact AF burden positively.

Rhythm-Control Strategies

Recent standards for AF emphasize holistic and individualized rhythm-control treatment. Sinus rhythm may be especially relevant in HFpEF patients, given that atrial contraction plays a crucial role in ventricular filling and exercise tolerance. The EAST-AFNET 4 trial was beneficial to patients with AF for early rhythm-control therapy in terms of cardiovascular status. Results are not limited to HFpEF, however, the implications are unambiguous for early intervention alternatives. For many selected symptomatic HFpEF patients with AF, catheter ablation has become an increasingly pertinent therapeutic option. Some possible benefits might include:

Improved symptoms and exercise capacity;

Reduction of AF burden;

Better quality of life;

Possible reduction in heart-failure hospitalization.

However, in HFpEF patients, advanced remodeling of the atria, obesity, sleep apnea, renal dysfunction and hypertension can often limit their chance of success. So aggressive risk-factor modification is considered necessary before and after rhythm-control measures.

Diagnostic Considerations

Diagnosing HFpEF in AF patients continues to be difficult. An elevated level of natriuretic peptide due to AF may also contribute to a poor clinical discriminative index, with its clinical significance related to AF. Beat-to-beat variability and abnormal filling dynamics also complicate the interpretation of echocardiography.

Key diagnostic parameters include:

Left atrial volume index (LAVI);

E/e' ratio;

Tricuspid regurgitation velocity;

Pulmonary artery pressure estimation;

Left ventricular mass index;

Global longitudinal strain (GLS);

Diastolic stress testing.

More advanced imaging methods are used to characterize the phenotype. Speckle tracking echocardiography may detect subtle atrial and ventricular failure well before more typical parameters become abnormal. Cardiac magnetic resonance imaging may supply valuable information on fibrosis, infiltration, and characterization of myocardial structures. The concept of functional atrial mitral regurgitation has also come into discussion among HFpEF and AF patients, caused by progressive atrial remodeling and annular dilatation.

DISCUSSION

The coexistence of HFpEF and AF is a major clinical issue due to mutual support for one another through hemodynamic, structural, inflammatory, and neurohormonal mechanisms. HFpEF treatment has historically targeted symptom control and management of comorbidities, which complicate the management of symptoms. The lack of effective disease-modifying therapies helped fuel the poor long-term outcomes. However, recent clinical trials have dramatically changed this therapeutic picture. Of all recent therapies, SGLT2 inhibitors have emerged as the best evidence-based treatment for HFpEF. These beneficial effects seem to be independent of diabetes status and involve hemodynamic, renal, anti-inflammatory, and metabolic pathways. Finerenone further expands the paradigm of targeted neurohormonal modulation in HFpEF. Its favourable cardiovascular effects point out that fibrosis and inflammation are important points in the pathophysiology of HFpEF. Another major development is the emergence of obesity-related HFpEF as a discrete and medicalizable phenotype. Semaglutide and tirzepatide showed significant improvement in symptoms, exercise output, and general life quality. These data highlight the central role of metabolic disturbance in HFpEF progression (9,10). The new paradigms for managing AF in HFpEF are moving towards earlier and more aggressive rhythm-control strategies for managing AF. Compared to prior evidence that favored a predominantly rate-directed approach to rate control, sinus rhythm maintenance may confer potential hemodynamic advantage in selected patients with

HFpEF (e.g., heart failure). (11,12) However, rhythm control interventions alone are usually inadequate if the underlying comorbidities are not treated. Obesity, hypertension, sleep apnea, diabetes mellitus, and renal insufficiency are highly implicated in atrial remodeling and AF regrowth. Integrated therapeutic management has been of growing significance.

Many evidence limitations remain. HFpEF is very heterogeneous, and in numerous clinical trials, there are large-scale patient populations with a wide phenotypic variability. Prospective work will presumably investigate further the more detailed phenotyping based on imaging, biomarkers, hemodynamic evaluation, and artificial intelligence-based methods. Furthermore, advanced imaging and analysis of atrial strain are becoming more important, along with invasive hemodynamic assessment. Currently, strong evidence supports a phenotype-oriented and individualized treatment strategy, rather than a uniform therapeutic approach.

CONCLUSIONS

FpEF and AF commonly coexist and are closely interconnected cardiovascular syndromes with severe morbidity and mortality. The management of HFpEF has greatly improved over recent years through therapeutic innovations in SGLT2 inhibition, with early support for finerenone and obesity-targeted agents (e.g., semaglutide, tirzepatide). Meanwhile, AF therapy continues to focus on early rhythm-control mechanisms and aggressive therapy of cardiovascular risk factors.An effective contemporary approach should include phenotype-guided HFpEF treatment, optimal management of comorbidities, appropriate anticoagulation based on thromboembolic risk, weight reduction in obese patients, and individualized rhythm-control strategies. Long-term multidisciplinary care is essential. Future progress will improve the identification of HFpEF phenotypes, enhance the understanding of atrial remodeling, and facilitate more personalized multimodal treatment strategies.

Conflict of interest: Nothing to declare.

Author contribution. All authors contributed to the preparation of the manuscript and approved the final version.

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REVIEW ARTICLE

WHEN TREATMENT BECOMES THE TRIGGER: POLYPHARMACY AS A HIDDEN CAUSE OF ACUTE CLINICAL DETERIORATION IN INTERNAL MEDICINE

Eneida Hoxha, Ledio Collaku, Somida Kuka, Pandush Pojani, Xhesika Habilaj, Margarita Gjata
Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding Email: eneida_hoxha@yahoo.com

ABSTRACT

Polypharmacy is increasingly common among older and multimorbid patients and represents one of the most frequent yet underrecognized challenges in internal medicine. Although traditionally defined as the concurrent use of five or more medications, its clinical relevance extends beyond the number of prescribed drugs. The risk emerges from the complex interaction between medications, comorbidities, organ dysfunction, frailty, acute illness, and changing therapeutic goals. In acute care settings, clinical deterioration is often attributed to disease progression, while the cumulative therapeutic burden may remain overlooked. This narrative clinical review aims to reframe polypharmacy as a hidden and potentially modifiable contributor to acute clinical deterioration in internal medicine. Particular attention is given to drug–drug and drug–disease interactions, renal impairment, hemodynamic vulnerability, electrolyte disturbances, bleeding risk, delirium, falls, and prescribing cascades. High-risk clinical phenotypes include patients with chronic kidney disease, heart failure, atrial fibrillation, diabetes, frailty, anemia, and acute infection. The review also emphasizes medication reconciliation, renal dose adjustment, structured prescribing tools such as STOPP/START and Beers Criteria and deprescribing as essential components of clinical reasoning. Polypharmacy should not be approached merely as a numerical threshold or a pharmacological problem, but as a dynamic clinical syndrome with diagnostic and therapeutic implications. Before escalating treatment or attributing deterioration solely to underlying disease, internists should ask whether treatment itself has become the trigger.

Keywords. Polypharmacy; Internal medicine; Multimorbidity; Deprescribing; Acute clinical deterioration

KUR TRAJTIMI BËHET SHKAKTAR: POLIFARMACIA SI SHKAK I FSHEHUR I PËRKEQËSIMIT AKUT KLINIK NË MJEKËSINË INTERNE.

ABSTRAKT

Polifarmacia është gjithnjë e më e shpeshtë te pacientët e moshuar dhe ata me multimorbiditet, duke përfaqësuar një nga sfidat më të zakonshme, por shpesh të

nënvlerësuara, në mjekësinë interne. Megjithëse tradicionalisht përkufizohet si përdorimi i njëkohshëm i pesë ose më shumë barnave, rëndësia e saj klinike shkon përtej numrit të medikamenteve të përshkruara. Rreziku lind nga ndërveprimi kompleks midis barnave, komorbiditeteve, disfunksionit të organeve, brishtësisë, sëmundjes akute dhe ndryshimit të objektivave terapeutikë. Në kujdesin akut, përkeqësimi klinik shpesh i atribuohet progresionit të sëmundjes, ndërkohë që barra terapeutike kumulative mund të mbetet e pavlerësuar. Ky rishikim narrativ klinik synon ta riformulojë polifarmacinë si një kontribues të fshehur dhe potencialisht të modifikueshëm në përkeqësimin klinik akut në mjekësinë interne. Vëmendje e veçantë i kushtohet ndërveprimeve bar-bar dhe bar-sëmundje, dëmtimit renal, vulnerabilitetit hemodinamik, çrregullimeve elektrolitike, rrezikut për hemorragji, deliriumit, rrëzimeve dhe kaskadave të përshkrimit medikamentoz. Fenotipet klinike me rrezik të lartë përfshijnë pacientët me sëmundje kronike renale, insuficiencë kardiake, fibrilacion atrial, diabet, sindromë të brishtësisë, anemi dhe infeksion akut. Rishikimi thekson gjithashtu rëndësinë e rakordimit të listës së barnave, përshtatjes së dozave sipas funksionit renal, mjeteve të strukturuara të përshkrimit si STOPP/START dhe Kriteret e Beers, si edhe depreskribimit (ndërprerja e strukturuar e barnave të panevojshme) si pjesë thelbësore e arsyetimit klinik. Polifarmacia nuk duhet të trajtohet thjesht si një prag numerik apo problem farmakologjik, por si një sindromë klinike dinamike me implikime diagnostike dhe terapeutike. Përpara përshkallëzimit të trajtimit ose atribuimit të përkeqësimit vetëm të sëmundjes bazë, internistët duhet të pyesin nëse vetë trajtimi është bërë shkaktari.

Fjalë kyç: Polifarmacia; Mjekësia interne; Multimorbiditeti; Reduktimi i barnave; Përkeqësimi
akut klinik.

INTRODUCTION

In internal medicine, acute clinical deterioration is often interpreted as the natural consequence of disease progression, advanced age, or multimorbidity. However, in older and clinically complex patients, deterioration may also result from the cumulative therapeutic burden imposed on a fragile physiological system. This distinction is clinically important because medication-related harm is potentially preventable, frequently underrecognized, and may mimic the progression of underlying disease (1-3).

Polypharmacy is commonly defined as the concurrent use of five or more medications, although definitions vary across studies and clinical settings (3,4). While this numerical threshold is useful for epidemiological purposes, it does not capture the full clinical complexity of medication-related risk. The relevance of polypharmacy depends not only on the number of prescribed drugs, but also on the interaction between medications, comorbidities, renal and hepatic function, frailty, acute illness, and therapeutic goals. Multiple evidence-based therapies may be justified, but they may become harmful when continued without reassessment, duplicated, poorly monitored, or used in combinations that increase the risk of adverse outcomes (3,5).

Patients admitted to internal medicine wards are particularly vulnerable because chronic kidney disease (CKD), heart failure (HF), diabetes mellitus (DM), atrial fibrillation (AF),

chronic obstructive pulmonary disease (COPD), anemia, frailty, recurrent infections, and cognitive impairment frequently coexist. These conditions reduce physiological reserve, alter pharmacokinetics and pharmacodynamics, and increase susceptibility to adverse drug events (2,6). Acute illness may further transform a previously tolerated medication regimen into a source of harm (1,2).

Medication safety has become a major international priority. The World Health Organization's *Medication Without Harm* initiative identifies polypharmacy, high-risk situations, and transitions of care as key areas for reducing avoidable medication-related harm (1,7). Structured tools such as STOPP/START version 3 and the 2023 American Geriatrics Society Beers Criteria provide practical frameworks for identifying potentially inappropriate medications in older adults (8,9).

This narrative clinical review examines polypharmacy as a hidden and potentially modifiable contributor to acute clinical deterioration in internal medicine. By reframing polypharmacy as a dynamic clinical syndrome rather than a simple medication count, internists may better recognize when treatment itself has become the trigger.

Polypharmacy beyond the number of medications

Polypharmacy should not be interpreted solely as the presence of multiple medications. In many patients with multimorbidity, the use of several drugs may be clinically appropriate when each medication has a clear indication, proven benefit, appropriate dosage, acceptable safety profile, and defined monitoring strategy. The central issue is therefore not the number of medications itself, but whether the therapeutic regimen remains coherent, individualized, and periodically reassessed (3).

The distinction between appropriate and inappropriate polypharmacy is therefore essential. Appropriate polypharmacy refers to the use of multiple medications when they are indicated, optimized, monitored, and aligned with the patient's current clinical condition and therapeutic goals. Inappropriate polypharmacy occurs when medications are unnecessary, duplicated, excessively dozed, poorly monitored, harmful in the context of comorbid disease, or no longer consistent with the patient's prognosis and priorities. The World Health Organization emphasizes that medication safety in polypharmacy requires systematic medication review, patient-centered prescribing, multidisciplinary collaboration, and attention to high-risk patients and transitions of care (1).

Medication burden is dynamic. A regimen that is appropriate in stable outpatient conditions may become unsafe during acute illness. Dehydration, infection, reduced oral intake, hypotension, acute kidney injury (AKI), liver dysfunction, or hospitalization may change the risk–benefit balance of previously tolerated medicate

ons. Diuretics, renin–angiotensin–aldosterone system inhibitors, anticoagulants, antidiabetic agents, sedatives, and non-steroidal anti-inflammatory drugs may all become harmful when physiological reserve declines or organ function changes (1,2,10).

Another important concept is the prescribing cascade. This occurs when an adverse drug effect is misinterpreted as a new medical condition, leading to the prescription of an additional medication rather than recognition of the original drug-related problem (11-13). In internal medicine, where nonspecific symptoms such as dizziness, confusion, edema, fatigue,

constipation, hypotension, and renal dysfunction are common, the risk of prescribing cascades is particularly high.

Thus, polypharmacy should be understood as a dynamic clinical condition rather than a fixed medication count. The key question is not only how many medications the patient is taking, but whether one or more of them could be contributing to the current deterioration.

Why internal medicine patients uniquely vulnerable

The internal medicine patient is rarely a single-disease patient. Most patients admitted to internal medicine wards present with overlapping chronic conditions, reduced physiological reserve, and acute stressors that interact with one another. Chronic kidney disease, heart failure, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, anemia, liver dysfunction, frailty, cognitive impairment, and recurrent infections often coexist, creating a clinical context in which medication safety becomes more complex than the evaluation of any single drug. Frailty, multimorbidity, and polypharmacy are closely interrelated and have been associated with higher healthcare use, unscheduled hospital admissions, and mortality (6,14).

This vulnerability is partly explained by altered pharmacokinetics and pharmacodynamics. Ageing and chronic disease are associated with reduced renal and hepatic clearance, altered drug distribution, increased sensitivity to central nervous system-active medications, impaired baroreflexes, and reduced homeostatic reserve. As a result, medications that are appropriate in stable or younger patients may produce exaggerated effects in older and frail individuals. Sedatives may precipitate delirium or falls, antihypertensives may cause orthostatic hypotension, anticholinergic drugs may worsen cognition or urinary retention, and diuretics may contribute to dehydration, electrolyte disorders, or renal dysfunction (2,9).

Renal impairment is one of the most important amplifiers of medication-related harm. Many commonly used drugs, including anticoagulants, antibiotics, antidiabetic agents, analgesics, digoxin, and cardiovascular medications, require dose adjustment or close monitoring in chronic kidney disease. KDIGO 2024 emphasizes drug stewardship in chronic kidney disease, including assessment of kidney function for drug dosing, avoidance of nephrotoxic agents when possible, and adjustment of medication use according to kidney function and clinical context (15). Importantly, renal function is not static during acute illness. Infection, hypovolemia, hypotension, contrast exposure, and nephrotoxic medications may transform stable chronic kidney disease into acute kidney injury, increasing the risk of drug accumulation and toxicity (15).

Heart failure illustrates the same tension between therapeutic benefit and vulnerability. Patients with heart failure often receive combinations of diuretics, renin–angiotensin–aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, sodium–glucose cotransporter 2 inhibitors, anticoagulants, and therapies for coexisting diseases. These treatments may be lifesaving in stable conditions, yet during acute illness, they may contribute to hypotension, renal dysfunction, electrolyte abnormalities, bradycardia, dehydration, or symptomatic intolerance. Thus, medication safety in internal medicine cannot be judged drug by drug in isolation; it must be interpreted dynamically within the whole clinical context.

Mechanisms by which treatment becomes the trigger

Polypharmacy contributes to acute deterioration through several overlapping mechanisms. In internal medicine, these mechanisms rarely act independently; they interact with multimorbidity, organ dysfunction, frailty, and acute physiological stress, making medication-related harm difficult to distinguish from disease progression (1-3).

Drug–drug and drug–disease interactions are central mechanisms. Pharmacokinetic interactions may alter absorption, metabolism, protein binding, or elimination, leading to reduced efficacy or toxicity, while pharmacodynamic interactions may produce additive effects such as sedation, hypotension, bleeding, bradycardia, or electrolyte imbalance. Drug–disease interactions are equally important: non-steroidal anti-inflammatory drugs (NSAIDs) may worsen hypertension, heart failure, gastrointestinal bleeding risk, and renal dysfunction; anticholinergic medications may aggravate cognitive impairment, constipation, urinary retention, and delirium; sedatives and hypnotics may increase the risk of falls, respiratory depression, and prolonged confusion. Polypharmacy has been associated with adverse drug events, drug–drug interactions, non-adherence, functional decline, cognitive impairment, falls, and hospitalization (2,16).

Renal and hemodynamic vulnerability represent another major pathway. Chronic kidney disease reduces drug clearance and narrows the therapeutic margin of many medications, while acute illness may rapidly worsen renal function and convert a previously tolerated regimen into a toxic one (15). The combination of renin–angiotensin–aldosterone system inhibitors, diuretics, and NSAIDs, commonly referred to as the “triple whammy”, is a classic example of treatment-related renal vulnerability and has been associated with increased risk of acute kidney injury (17,18). Similarly, antihypertensives, diuretics, vasodilators, beta-blockers, nitrates, and heart failure therapies may be beneficial in stable chronic disease but may contribute to hypotension, syncope, renal hypoperfusion, or falls during sepsis, reduced oral intake, diarrhea, bleeding, or dehydration.

The clinical expressions of harmful polypharmacy are often nonspecific. Electrolyte disturbances, hypoglycemia, bleeding, and neurocognitive effects may present as weakness, confusion, falls, arrhythmia, hypotension, or functional decline. Hyperkalemia, hyponatremia, hypoglycemia, occult bleeding, and delirium may therefore be interpreted as isolated clinical problems unless the medication regimen is reviewed as a potential contributor (2,5,6).

A final and frequently overlooked mechanism is the prescribing cascade. This occurs when an adverse drug effect is misinterpreted as a new clinical condition, prompting the addition of another medication rather than recognition and correction of the original drug-related problem. Calcium-channel blocker-induced edema may lead to unnecessary diuretic therapy; drug-induced dizziness may be interpreted as a neurological disorder; and sedative-related confusion may be treated as worsening dementia or infection. Prescribing cascades are increasingly recognized as contributors to inappropriate polypharmacy, particularly among older adults (11-13).

For the internist, these mechanisms should shift diagnostic reasoning from a single question, that disease explains deterioration, to a broader one: which treatment, interaction, or therapeutic accumulation could be contributing to it?

High-risk clinical phenotypes in internal medicine

Harmful polypharmacy does not occur randomly. In internal medicine, it often emerges from recognizable clinical phenotypes in which multimorbidity, organ dysfunction, acute stressors, and high-risk medication clusters converge. Identifying these patterns may help internists move beyond a passive review of medication lists toward a targeted search for treatment-related harm.

One common phenotype is the patient with chronic kidney disease, hypertension, and heart failure receiving multiple cardiovascular and renal protective therapies. Renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, sodium–glucose cotransporter 2 inhibitors, and diuretics may provide substantial long-term benefit. However, during dehydration, infection, hypotension, or acute kidney injury, these same therapies may contribute to renal hypoperfusion, hyperkalemia, volume depletion, or symptomatic hypotension. The addition of NSAIDs further increases the risk of acute kidney injury, particularly in patients already receiving a renin–angiotensin system inhibitor and a diuretic (15,17).

Other vulnerable phenotypes include patients with atrial fibrillation, coronary artery disease, chronic kidney disease, or anemia receiving antithrombotic therapy; frail older adults exposed to central nervous system-active or anticholinergic medications; patients with diabetes mellitus and declining renal function treated with insulin or sulfonylureas; patients with chronic pain, chronic kidney disease, heart failure, or hypertension exposed to NSAIDs; and patients undergoing transitions of care, when medications may be duplicated, omitted, or unintentionally restarted. Antithrombotic combinations require particular attention because bleeding risk is amplified by advanced age, renal disease, anemia, prior bleeding, falls, and concomitant NSAID or antiplatelet use (8,19).

These patterns illustrate that harmful polypharmacy often arises from predictable combinations of vulnerable patients, acute stressors, and medication clusters. Recognizing them transforms medication review into a clinically directed diagnostic intervention.

Table 1. High-risk polypharmacy phenotypes in internal medicine

Clinical phenotype	High-risk medication cluster	Potential deterioration	Key clinical action
CKD + hypertension + HF	RAAS inhibitors + diuretics ± MRA ± NSAIDs	AKI, hyperkalemia, hypotension	Check renal function, potassium and volume status; reassess NSAIDs and temporarily unsafe combinations
AF + CAD + CKD/anemia	Anticoagulant + antiplatelet ± NSAID	Bleeding, anemia, hypotension	Reassess indication, dose, duration, renal adjustment and bleeding risk
Frail older adult	Benzodiazepines, hypnotics, opioids, anticholinergics	Delirium, falls, sedation	Reduce CNS-active drugs and anticholinergic burden; consider deprescribing
DM + CKD/acute illness	Insulin or sulfonylureas during reduced intake or renal decline	Hypoglycemia, confusion, falls	Adjust therapy to renal function, oral intake and glycemic trends
Chronic pain + CKD/HF/hypertension	NSAIDs ± RAAS inhibitors ± diuretics	AKI, fluid retention, gastrointestinal bleeding	Avoid or minimize NSAIDs; choose safer analgesia
Admission/discharge transition	Duplicated, omitted, or unintentionally restarted medications	Toxicity, undertreatment, readmission	Perform medication reconciliation at every transition

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; CAD, coronary artery disease; CKD, chronic kidney disease; CNS, central nervous system; DM, diabetes mellitus; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system.

Polypharmacy in acute internal medicine

In the emergency department and acute medical ward, polypharmacy may become both a diagnostic challenge and a therapeutic hazard. Patients are frequently admitted with nonspecific manifestations such as confusion, falls, hypotension, acute kidney injury, electrolyte disturbances, bleeding, bradycardia, hypoglycemia, or functional decline. These presentations are often attributed to infection, dehydration, ageing, or progression of chronic disease, while medication-related harm may remain insufficiently explored (2,5,6).

Medication history should therefore be considered a diagnostic intervention, not merely an administrative task. A structured review of prescribed drugs, over-the-counter medications, herbal products, recent dose changes, adherence patterns, and newly introduced therapies may reveal clinically relevant triggers. Particular attention should be given to medications initiated shortly before deterioration, drugs requiring renal dose adjustment, combinations associated with hypotension or bleeding, and agents with central nervous system or anticholinergic effects (1,4,20).

Acute illness can rapidly change the safety profile of chronic treatment. Sepsis, vomiting, diarrhea, reduced oral intake, dehydration, hypotension, and acute kidney injury may transform a previously appropriate regimen into a source of harm. During hospitalization, therapeutic plans are often modified by multiple clinicians, increasing the risk of duplication, omission, inappropriate continuation, or unintentional re-prescribing. These risks are especially important at admission and discharge, when medication reconciliation may be incomplete or fragmented. Medication reconciliation has therefore been emphasized as a key safety strategy during transitions of care (4,20).

In acute care, the central question should not be limited to which new diagnosis explains deterioration. It should also include whether one or more medications could be contributing to the current presentation. In acute internal medicine, medication review should be triggered not only by admission or discharge, but by any unexplained deterioration.

Deprescribing and safer prescribing: a structured approach for the internist

Deprescribing should not be understood as simple medication withdrawal, but as a structured process of clinical reasoning aimed at improving safety, reducing harm, and aligning treatment with the patient's current condition, prognosis, and goals of care. It has been defined as the planned and supervised process of dose reduction or discontinuation of medications that may be causing harm or may no longer provide meaningful benefit (10,21). The objective is not to reduce medication numbers indiscriminately, but to identify therapies whose risks exceed their benefits, whose indication is no longer valid, or whose continuation has become unsafe in the context of acute illness, frailty, organ dysfunction, or limited physiological reserve.

Several structured tools may support this process. STOPP/START criteria provide an explicit framework for identifying potentially inappropriate medications and clinically indicated treatments that may be omitted, while the American Geriatrics Society Beers Criteria help recognize medications associated with delirium, falls, cognitive impairment, anticholinergic burden, bleeding risk, and renal dosing concerns in older adults (7,8). Anticholinergic burden is particularly relevant in frail older patients, as it has been associated with delirium and other adverse neurocognitive outcomes (22,23). These tools are useful for standardizing medication review, but they should not be applied mechanically. A medication may be inappropriate in one clinical context, temporarily necessary in another, or safe only under close monitoring.

For the internist, medication review should be structured, repeated, and clinically triggered. First, obtain an accurate medication history, including prescription drugs, over-the-counter medications, herbal products, recent dose changes, adherence patterns, and medications prescribed by different specialists. Second, identify high-risk drugs and combinations,

particularly anticoagulants, antiplatelet agents, diuretics, renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, insulin, sulfonylureas, NSAIDs, opioids, benzodiazepines, anticholinergics, and drugs requiring renal dose adjustment. Third, evaluate whether one or more medications could plausibly contribute to the current presentation, such as delirium, falls, hypotension, acute kidney injury, electrolyte imbalance, bleeding, hypoglycemia, or functional decline. Finally, decide whether treatment should becontinued, monitored, reduced, substituted, temporarily withheld, or discontinued (16,21).Clear documentation and communication across transitions of care are essential to avoid unintentional re-prescribing, therapeutic omission, or abrupt discontinuation without follow-up (4,20). In this framework, deprescribing is not therapeutic nihilism; it is a safety-oriented intervention that complements evidence-based prescribing. Medication review becomes a proactive diagnostic and therapeutic intervention rather than a retrospective safety exercise.

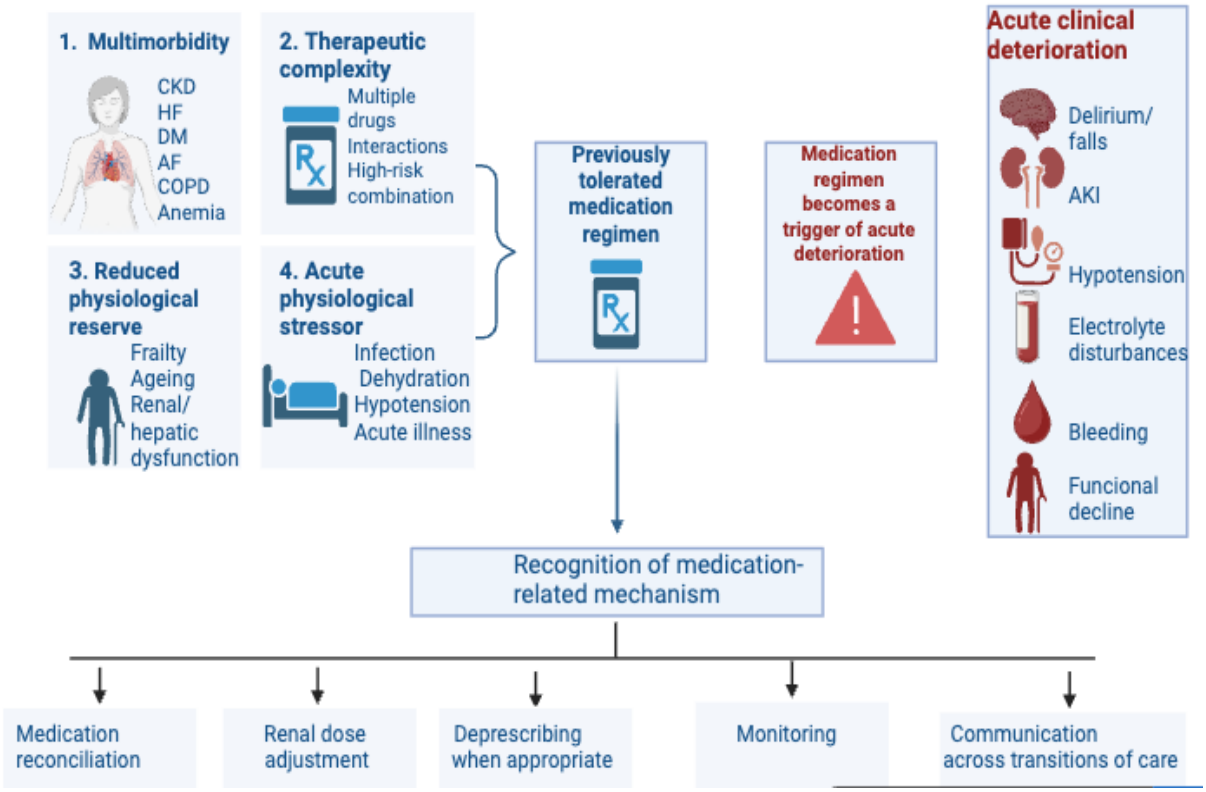


Figure 1. The Internal Medicine Polypharmacy Trigger Model**.** Polypharmacy-related harm in internal medicine emerges from the interaction between multimorbidity, therapeutic complexity, reduced physiological reserve, and acute physiological stressors. These factors may transform a previously tolerated medication regimen into a trigger of acute deterioration. Recognition of medication-related mechanisms should prompt structured medication reconciliation, renal dose adjustment, deprescribing when appropriate, monitoring, and clear communication across transitions of care.

DISCUSSION

Reframing polypharmacy as a clinical syndrome in internal medicine

Polypharmacy is often approached as a medication count, but in internal medicine, its clinical significance is broader and more dynamic. The central question is not simply whether a patient is taking five, eight, or ten medications, but whether the therapeutic regimen remains appropriate in the context of multimorbidity, organ dysfunction, frailty, acute illness, and evolving goals of care. This reframing shift polypharmacy from a pharmacological label to a clinical syndrome with diagnostic and therapeutic implications (1-3,16).

This perspective is particularly relevant in acute care, where medication-related harm may present nonspecific manifestations such as confusion, falls, hypotension, acute kidney injury, electrolyte disturbances, bleeding, anemia, bradycardia, hypoglycemia, or functional decline. These presentations are often attributed to infection, ageing, frailty, or progression of chronic disease, while the contribution of medications may be considered only after other causes have been excluded. Evaluating treatment-related deterioration early, in parallel with other diagnostic hypotheses, may reduce preventable harm and avoid unnecessary therapeutic escalation (1,2,6).

Importantly, this approach does not imply that complex patients should receive fewer medications by default. Many patients with heart failure, chronic kidney disease, diabetes mellitus, atrial fibrillation, or coronary artery disease benefit from multiple evidence-based therapies. The clinical challenge is to distinguish beneficial therapeutic complexity from harmful therapeutic burden. Appropriate polypharmacy requires indication, proportionality, monitoring, and reassessment. Inappropriate polypharmacy emerges when prescriptions accumulate without systematic review, adverse effects are treated as new diseases, organ function changes without dose adjustment, or treatment goals are no longer aligned with clinical reality (3,8,10).

The internist has a central role because internal medicine is the discipline of integration. Unlike single-disease approaches, internal medicine must interpret the whole patient: diseases, drugs, physiology, prognosis, function, and priorities. In this context, medication review is not a secondary administrative task, but a core component of clinical reasoning. Before adding another drug, escalating treatment, or attributing deterioration solely to disease progression, clinicians should ask whether the current therapeutic regimen may be contributing to the problem (24).

Digital tools and clinical decision support systems may help identify interactions, renal dosing problems, duplication, and high-risk combinations; however, they cannot replace clinical judgment. The final decision must remain individualized and anchored in the patient's current condition. Ultimately, reframing polypharmacy as a clinical syndrome does not weaken evidence-based medicine; it strengthens it. It reminds clinicians that evidence must be applied to a person, not only to a disease. In complex internal medicine patients, the safest treatment is not always the longest medication list, but the most coherent one (24).

CONCLUSIONS

Polypharmacy is one of the most frequent yet underrecognized challenges in internal medicine. Although often defined by the number of prescribed medications, its true clinical relevance lies in the interaction between drugs, diseases, organ function, frailty, acute illness, and therapeutic goals. In older and multimorbid patients, treatment itself may become a hidden trigger of acute deterioration, presenting as delirium, falls, hypotension, acute kidney injury, bleeding, electrolyte disorders, hypoglycemia, or functional decline.

For internists, medication review should be considered an essential part of diagnostic reasoning, particularly during acute deterioration, hospitalization, and transitions of care. Structured approaches such as medication reconciliation, renal dose adjustment, STOPP/START criteria, Beers Criteria, and deprescribing can support safer prescribing when applied within an individualized clinical context.

Polypharmacy should therefore be approached not merely as a pharmacological problem, but as a dynamic and potentially modifiable clinical syndrome. Before escalating therapy or attributing deterioration solely to disease progression, clinicians should ask whether treatment itself has become the trigger.

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INTENSIVE CARE MANAGEMENT OF PATIENTS WITH SCLERODERMA: A CASE SERIES

Dorina Ruci[1], Krisli Serani[2], Vilson Ruci[3], Arsel Dizdari[4], Entela Shkodrani[5]
[1] Rheumatology Department, University Hospital Center "Mother Teresa", Tirana, Albania
[2] Anesthesia and Intensive Care Department, University Hospital Center "Mother Teresa", Tirana, Albania
[3] Orthopedics Department, University Hospital of Trauma, Tirana, Albania
[4] Orthopedics Department, Regional Memorial Hospital, Fier, Albania
[5] Dermatology Department, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding E-mail: dorinaruci25@gmail.com

ABSTRACT

Background. Systemic sclerosis (scleroderma) is a chronic autoimmune disease characterized by immune activation, vasculopathy, and progressive fibrosis, frequently leading to multi-organ involvement. Pulmonary, renal, and cardiac complications are associated with high mortality, particularly in intensive care settings.
Aim. To present three clinical cases of advanced systemic sclerosis managed in the intensive care unit (ICU) and to analyze the therapeutic strategies applied, clinical challenges encountered, and the role of a multidisciplinary approach in improving outcomes.
Methods. We conducted a retrospective analysis of three patients with severe systemic sclerosis complications treated in a tertiary ICU over 18 months. Data was obtained from medical records, laboratory and imaging findings, and multidisciplinary consultation reports.
Results. Case 1 involved severe pulmonary hypertension with acute respiratory failure, successfully managed with mechanical ventilation, inhaled Iloprost, and cyclophosphamide. Case 2 presented with scleroderma renal crisis requiring high-dose ACE inhibitors and emergency dialysis, resulting in partial renal recovery. Case 3 developed malignant ventricular arrhythmias managed with ICD implantation and antiarrhythmic therapy, leading to rhythm stabilization. Early aggressive intervention, invasive monitoring, and coordinated multidisciplinary management were decisive in all cases. All three patients survived the critical phase and were successfully transferred to the ward.
Conclusions. Intensive management of systemic sclerosis complications requires prompt recognition, individualized therapy, and close multidisciplinary collaboration. Early aggressive intervention in the ICU may significantly improve short-term survival and clinical stabilization in patients with life-threatening organ involvement.
Keywords. systemic sclerosis, scleroderma, intensive care, pulmonary hypertension, renal crisis, ventricular arrhythmia, multidisciplinary management.

MENAXHIMI NË TERAPI INTENSIVE I PACIENTËVE ME SKLEROZË SISTEMIKE: SERI RASTESH

ABSTRAKT

Hyrje. Skleroderma (skleroza sistemike) është një sëmundje autoimune kronike e karakterizuar nga aktivizimi imunitar, vaskulopatia dhe fibroza progresive, që shpesh çon në përfshirje multiorganike. Komplikacionet pulmonare, renale dhe kardiake shoqërohen me mortalitet të lartë, veçanërisht në kushtet e terapisë intensive.
Qëllimi. Të paraqiten tre raste klinike me sklerozë sistemike të avancuar të trajtuara në njësinë e terapisë intensive dhe të analizohet strategjia terapeutike, sfidat klinike dhe roli i bashkëpunimit multidisiplinar në përmirësimin e rezultateve.
Metoda. U realizua një analizë retrospektive e tre pacientëve me komplikacione të rënda nga skleroza sistemike, të trajtuar në një qendër terciare gjatë një periudhe 18-mujore. Të dhënat u morën nga kartelat mjekësore, ekzaminimet laboratorike dhe imazherike, si dhe nga raportet e konsultave multidisiplinare.
Rezultate. Rasti i parë paraqiti hipertension pulmonar të rëndë me insuficiencë respiratore akute, i menaxhuar me ventilim mekanik, iloprost inhalator dhe ciklofosfamid. Rasti i dytë zhvilloi krizë renale nga skleroderma, e trajtuar me inhibitorë ACE në doza të larta dhe dializë emergjente, me rikuperim parcial të funksionit renal. Rasti i tretë u paraqit me aritmi ventrikulare malinje dhe u trajtua me implantim ICD dhe terapi antiaritmike, duke arritur stabilizim ritmik. Ndërhyrja e hershme agresive, monitorimi invaziv dhe bashkëpunimi multidisiplinar ishin vendimtare në të tre rastet. Të gjithë pacientët mbijetuan fazën kritike dhe u transferuan në repart.
Përfundime. Menaxhimi intensiv i komplikacioneve të sklerozës sistemike kërkon diagnostikim të hershëm, terapi të individualizuar dhe bashkëpunim të ngushtë multidisiplinar. Ndërhyrja e hershme në terapi intensive mund të përmirësojë ndjeshëm mbijetesën afatshkurtër dhe stabilizimin klinik te pacientët me përfshirje të rrezikshme multiorganike.

Fjalë kyçe. skleroza sistemike, skleroderma, terapi intensive, hipertension pulmonar, krizë renale, aritmi ventrikulare, qasje multidisiplinare.

INTRODUCTION

Scleroderma (systemic sclerosis) is a chronic, progressive, systemic autoimmune disease characterized by three main pathological mechanisms: immune activation, vasculopathy, and progressive fibrosis of the skin and internal organs (1). Its prevalence ranges from 50 to 300 cases per million population, with a marked female predominance (female-to- male ratio 3-5:1). The peak incidence typically occurs between the fourth and sixth decades of life. Pathogenesis involves a complex interaction between genetic, immunologic, and environmental factors. Activation of T and B lymphocytes, production of specific autoantibodies (such as anti-Scl-70 and anti-centromere), endothelial dysfunction, and excessive collagen deposition by fibroblasts are key elements in disease development (1).

The result is a combination of progressive fibrosis, vascular damage, and chronic inflammation, leading to multi-organ dysfunction.
Clinically, scleroderma is classified into limited, diffuse, and sine scleroderma forms, depending on the extent of skin involvement and internal organ involvement (1).
Pulmonary involvement (interstitial lung disease and pulmonary hypertension), cardiac involvement (arrhythmias and heart failure), and renal involvement (scleroderma renal crisis) are associated with high mortality, particularly in intensive care settings (1). In intensive care units (ICUs), patients with scleroderma often present with life-threatening complications.
Management represents a major challenge due to the complexity of the disease, clinical heterogeneity, and lack of standardized treatment protocols (2,3). Early intervention, invasive monitoring, and a multidisciplinary approach among rheumatologists, anesthesiologists, cardiologists, nephrologists, and pulmonologists are crucial for improving survival and quality of life (5).
This article aimed to present three clinical cases of patients with advanced systemic scleroderma treated in the intensive care unit over 18 months and to analyze the therapeutic approach used for each patient and the clinical challenges encountered during treatment, as well as the decisive role of a multidisciplinary approach in improving clinical outcomes. These case series also aimed to contribute to existing literature by providing practical experience in the intensive management of patients with scleroderma and by emphasizing the importance of early diagnosis and intervention.

MATERIALS AND METHODS

This is a retrospective study including three patients with advanced systemic scleroderma who were treated in the intensive care unit of a tertiary hospital center, over 18 months. Case selection was based on the presence of severe complications requiring immediate multidisciplinary intervention. Data was obtained from medical records, intensive monitoring reports, laboratory and imaging examinations, and daily multidisciplinary consultation assessments.

Case 1: *Severe Pulmonary Involvement*
Patient: Female, 47 years old.
Clinical presentation: Severe pulmonary hypertension, acute respiratory failure, profound hypoxemia, and elevated coagulation markers (D-dimer).
Treatment: Invasive mechanical ventilation with parameters adapted according to ARDS protocols. Administration of inhaled Iloprost as vasodilator therapy. Intravenous cyclophosphamide was administered to suppress the autoimmune process. Gradual oxygen support and continuous monitoring of arterial blood gases.
Clinical course: The patient showed gradual improvement in oxygenation following mechanical ventilation and immunomodulatory therapy with cyclophosphamide. Transfer to the ward was carried out after respiratory stabilization, demonstrating the effectiveness of early intensive intervention.

Case 2:*Scleroderma Renal Crisis*
Patient: Male, 52 years old.

Clinical presentation: Scleroderma renal crisis with anuria, severe and refractory hypertension, uremia, and progressively increasing azotemia.
Treatment: Immediate initiation of high-dose ACE inhibitors as standard therapy for scleroderma renal crisis. Emergency dialysis for correction of metabolic disturbances and management of hypervolemia. Invasive monitoring of fluid balance and renal function.
Clinical course: Despite the immediate initiation of ACE inhibitors and emergency dialysis, the patient exhibited a slow clinical course; however, partial recovery of diuresis and reduction of blood pressure after several days demonstrated the vital role of invasive monitoring and multidisciplinary therapy.

Case 3:*Cardiac Involvement - Ventricular Arrhythmias*
Patient: Female, 39 years old.
Clinical presentation: Recurrent ventricular arrhythmias, palpitations, and syncope. Echocardiography showed myocardial fibrosis.
Treatment: Implantation of an ICD (Implantable Cardioverter Defibrillator) for the prevention of sudden death due to malignant arrhythmias. Initiation of antiarrhythmic therapy with amiodarone. Electrolyte correction and strict balance monitoring.
Clinical course: ICD implantation and antiarrhythmic therapy led to rapid stabilization of cardiac rhythm, with no recurrence of arrhythmia during the ICU stay.

Shared Clinical Features
Early intervention was decisive in all three cases. Patients who received aggressive and multidisciplinary treatment in the first hours had a more favorable clinical course. Continuous invasive monitoring (arterial blood gases, pulmonary pressure, fluid balance, cardiac parameters) proved essential in preventing further complications.
The multidisciplinary approach emerged as a key factor: each therapeutic decision was made collaboratively among the rheumatologist, intensivist, cardiologist, and nephrologist, ensuring safer and more individualized management. Immunomodulatory and supportive therapy (Cyclophosphamide, Iloprost, ACE inhibitors, antiarrhythmics) had positive effects in all three cases, highlighting the importance of integrating targeted treatments with intensive care measures.
Survival and Quality of Care: All three patients survived the critical period and were transferred from the ICU to the ward for further treatment. This outcome reinforces the concept that early diagnosis and coordinated intervention can significantly improve the prognosis of patients with advanced systemic sclerosis.

DISCUSSION

Systemic sclerosis remains one of the most complex diseases within the group of rheumatologic disorders, with high mortality when vital organs are involved (5). Pulmonary, cardiac, and renal involvement are determining factors for clinical outcomes and often necessitate intensive therapy. Our cases clearly illustrate that managing patients with such complications requires rapid intervention and close multidisciplinary coordination (3).
Pulmonary Involvement

Pulmonary hypertension and interstitial fibrosis represent the most frequent and severe pulmonary complications in systemic sclerosis (4). Previous studies have shown that mortality among patients with pulmonary hypertension reaches up to 40–50% within five years (2). In our case, the 47-year-old patient benefited from the combination of mechanical ventilation and targeted therapy with Iloprost, supported by immunotherapy with cyclophosphamide. The literature suggests that early intervention with vasodilator agents, in accordance with current ESC/ERS pulmonary hypertension guidelines, and immunosuppressive therapy may improve oxygenation and long-term prognosis (4,9).

Scleroderma Renal Crisis

Renal crisis occurs in approximately 5–10% of patients with diffuse systemic sclerosis and is characterized by sudden-onset hypertension, acute renal failure, and often high mortality (3). ACE inhibitors have revolutionized the treatment of this condition and remain the first-line therapy according to current international guidelines, significantly reducing mortality (7,10). In our case, the immediate administration of ACE inhibitors and initiation of emergency dialysis resulted in partial recovery of renal function (7).

Cardiac Involvement

Ventricular arrhythmias and myocardial fibrosis pose a major challenge. ICD implantation in patients with malignant arrhythmias is a life-saving intervention (2).

Antiarrhythmic therapy and electrolyte correction are essential components of short-term stabilization (5).

Importance of the Multidisciplinary Approach

Therapeutic decisions were made in close collaboration among rheumatologists, anesthesiologists, cardiologists, and nephrologists. This coordination reflects the benefits of a multidisciplinary approach (3). International literature supports this model, suggesting that structured interdisciplinary collaboration improves survival and quality of life in patients with systemic autoimmune diseases (4).

Meta-analytic studies have shown that patients with connective tissue diseases treated in the ICU have an average mortality rate of 40–50%, particularly in the presence of multi-organ complications (5). In our cases, all three patients survived the critical period and were transferred from the ICU to the ward, suggesting that early diagnosis, aggressive intervention, and a multidisciplinary approach may significantly reduce this mortality rate (2). These findings emphasize that structured ICU protocols and early targeted therapy may alter the traditionally poor prognosis associated with systemic sclerosis-related multi-organ failure.

Clinical Challenges

Based on our experience and literature, several major challenges emerge:

- Early diagnosis is often delayed due to the clinical variability of the disease.
- Hidden comorbidities (e.g., hypertension, subclinical heart failure) may worsen prognosis.
- Short-term versus long-term management: intensive intervention saves lives but does not always address the progression of fibrosis and chronic organ involvement.
- The use of immunotherapy in critically ill patients remains an area with many uncertainties, requiring careful individualization.

This article has several limitations that should be considered when interpreting the results. First, the sample size is small (only three cases), making it impossible to draw general conclusions about the entire scleroderma population. Second, the retrospective nature of the analysis limits control over clinical and therapeutic variables. Third, long-term follow-up after ICU discharge was not fully included in this report, limiting the assessment of therapy effects on quality of life and long-term survival. Nevertheless, despite these limitations, case presentations provide valuable insight into the challenges and strategies of intensive management in patients with scleroderma.

FUTURE PERSPECTIVES

Based on our experience and international literature, future efforts should focus on:

- Developing prospective studies with larger patient cohorts to more systematically evaluate the impact of multidisciplinary care on survival.
- Establishing ICU-specific clinical guidelines based on scientific evidence regarding immunotherapy and targeted treatments.
- Integrating new technologies such as non-invasive hemodynamic monitoring, serological biomarkers, and advanced imaging for earlier detection of organ involvement.
- Promoting international collaboration among major academic centers to create shared registries and clinical databases for patients with scleroderma in the ICU.

CONCLUSIONS

Systemic sclerosis with severe organ involvement remains a life-threatening condition requiring prompt recognition and aggressive management. Our case series highlights that early admission to the intensive care unit, rapid initiation of targeted therapy, and continuous invasive monitoring are critical for short-term survival in patients with pulmonary, renal, and cardiac complications.

A coordinated multidisciplinary approach involving rheumatologists, intensivists, cardiologists, and nephrologists plays a decisive role in optimizing clinical outcomes. Although limited by the small number of cases, our experience supports the concept that early aggressive and individualized intensive care management can significantly improve stabilization and survival in critically ill patients with systemic sclerosis.

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Patient Consent: Written informed consent was obtained from the patients (or their legal guardians) for publication of the clinical data and identifiable clinical images.

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THE ROLE OF VIDEONYSTAGMOGRAPHY AND MAGNETIC RESONANCE IMAGING IN RECURRENT POSITIONAL VERTIGO: A CASE REPORT

Evis Bendo[1], Nirian Bendo[2]

[1]ENT Department, University Hospital Center "Mother Teresa", Tirana, Albania
[2]Trauma Hospital, Tirana, Albania
Corresponding E-mail: drbendo@gmail.com

ABSTRACT

Background. Benign paroxysmal positional vertigo (BPPV) is the most frequent cause of positional vertigo and usually responds well to canalith repositioning maneuvers. Atypical clinical features should raise suspicion for central nervous system pathology.
Case presentation. We present a 64-year-old male with recurrent positional vertigo initially diagnosed as posterior canal BPPV. Dix–Hallpike testing elicited transient torsional geotropic nystagmus, and symptoms initially resolved after an Epley maneuver. One month later, vertigo recurred, and repeated repositioning maneuvers resulted only in partial improvement. Cranial magnetic resonance imaging revealed a posterior fossa intracranial lesion. The patient underwent neurosurgical treatment and was symptom-free at follow-up.
Conclusion. Early recurrence and incomplete response to repositioning maneuvers are red flags for central positional vertigo. High-resolution magnetic resonance imaging of the posterior fossa is recommended in such cases.
Keywords. benign paroxysmal positional vertigo; central positional nystagmus; magnetic resonance imaging; vestibular rehabilitation

ROLI I VIDEONISTAGMOGRAFISË DHE REZONANCËS MAGNETIKE NË VLERËSIMIN E VERTIGOS POZICIONALE TË PËRSËRITUR: RAPORTIM RASTI

ABSTRAKT

Hyrje. Vertigo paroksizmale beninje pozicionale është shkaku më i shpeshtë i vertigos pozicionale dhe zakonisht trajtohet me sukses me manovrat e ripozicionimit të kanaloliteve. Tiparet atipike klinike duhet të ngrenë dyshimin për patologji qendrore.
Prezantimi i rastit. Paraqitet rasti i një mashkulli 64-vjeçar me vertigo pozicionale të përsëritur, fillimisht e diagnostikuar si BPPV e kanalit posterior. Testi Dix–Hallpike shkaktoi nistagmus torsional gjeotropik kalimtar dhe simptomat u përmirësuan pas manovrës Epley. Një muaj më vonë u shfaq rikthimi i vertigos dhe manovrat e përsëritura sollën vetëm përmirësim të pjesshëm. Rezonanca magnetike kraniale zbuloi një lezion intrakranial në fossën posteriore. Pacienti iu nënshtrua ndërhyrjes neurokirurgjikale dhe në ndjekje rezultoi pa simptoma.

Përfundimi. Rikthimi i hershëm dhe përgjigjja jo e plotë ndaj manovrave të ripozicionimit përfaqësojnë shenja alarmi për vertigo pozicionale qendrore. Rekomandohet MRI me rezolucion të lartë e fossës posteriore.
Fjalë kyç. vertigo pozicionale beninje; nistagmus pozicional qendror; rezonancë magnetike

INTRODUCTION

Benign paroxysmal positional vertigo accounts for approximately 80% of positional vertigo cases, with posterior semicircular canal involvement in 80–90% of patients. [2,3] It is characterized by brief vertigo triggered by head position changes and a typical positional nystagmus during the Dix–Hallpike maneuver, showing latency, a torsional upbeat component, and fatigability.[4,9]

Most patients respond successfully to canalith repositioning maneuvers and do not require further investigations. [4,6] However, certain findings, such as absence of latency, lack of fatigability, pure vertical nystagmus, minimal vertigo during testing, and poor therapeutic response, suggest central nervous system involvement. [5,10] Between 12% and 20% of positional vertigo cases may have a central origin.[1] This report highlights the importance of differentiating peripheral BPPV from central positional vertigo.

CASE PRESENTATION

A 64-year-old male presented with several months of positional vertigo, particularly when turning in bed to the left. His past medical history was unremarkable. Otoscopy was normal. Pure-tone audiometry showed mild high-frequency sensorineural hearing loss in the right ear and normal hearing in the left ear. Videonystagmography demonstrated normal gaze, saccadic, and oculomotor tests. The Dix–Hallpike maneuver elicited transient rotatory geotropic left-beating nystagmus. An Epley maneuver was performed, with complete symptom resolution at one-week follow-up.

One month later, the patient returned with recurrent vertigo. Dix–Hallpike testing remained positive, eliciting rotatory geotropic nystagmus. Repeated Epley maneuver resulted in only partial improvement, and the Semont maneuver was ineffective.

Due to an incomplete therapeutic response and early recurrence, cranial magnetic resonance imaging was performed, revealing a lesion in the posterior fossa. The case was referred to the neurosurgery department, where the patient underwent total resection with intraoperative EMG monitoring. Histopathological examination of the biopsy confirmed a meningioma.

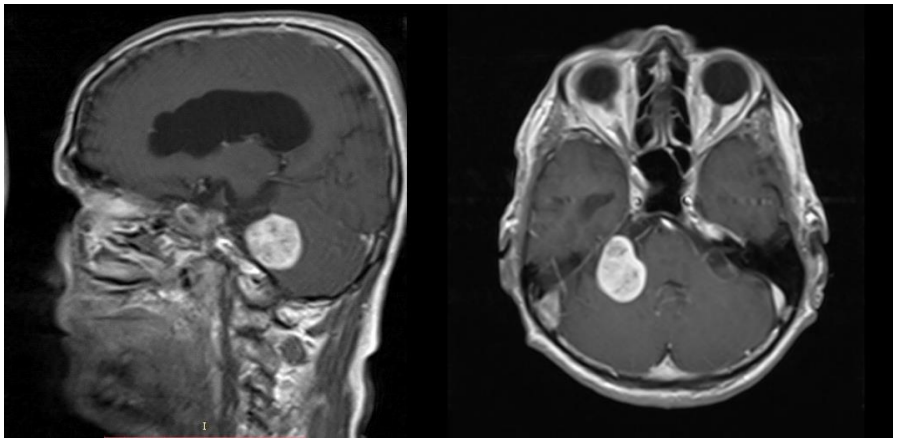


Figure 1. Preoperative MRI showing an intracranial lesion in the posterior fossa.

The patient underwent neurosurgical intervention (Figure 2). At the ENT follow-up, he remained asymptomatic.

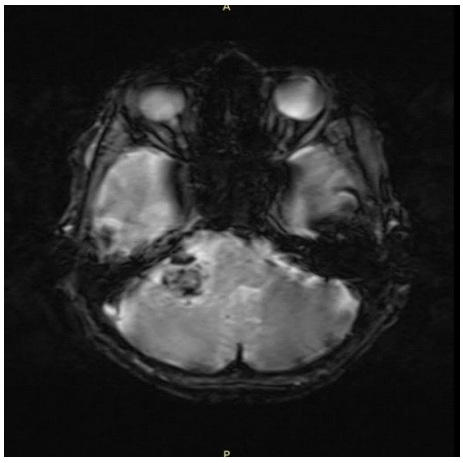


Figure 2. Postoperative MRI after neurosurgical intervention.

DISCUSSION

Central lesions may closely mimic BPPV, and early recurrence or poor response to repositioning maneuvers may be the only warning signs [5,10].

Although horizontal canal variants and cupulolithiasis can present with atypical features, [7,8] persistent, non-fatigable, or purely vertical positional nystagmus strongly suggests central pathology [10]. Central paroxysmal positional nystagmus has distinct mechanisms compared with peripheral BPPV and is frequently associated with cerebellar or brainstem lesions [10]. Posterior fossa lesions, particularly cerebellar tumors, are well-recognized causes of central positional vertigo and are frequently associated with downbeat nystagmus.

Magnetic resonance imaging is the diagnostic modality of choice when posterior fossa pathology is suspected, as computed tomography has limited sensitivity in this region.[11]

Clinical practice guidelines recommend against routine imaging in typical BPPV but strongly support further evaluation when atypical features or treatment failure occur [4,9].

This case underlines the importance of neuroimaging in patients with recurrent or partially responsive positional vertigo and demonstrates how central pathology may initially mimic peripheral vestibular disease.

CONCLUSION

The diagnosis of BPPV should be established only when positional testing demonstrates nystagmus with characteristic peripheral features. Certain findings should raise suspicion for central pathology. These include the absence of latency, lack of fatigability, pure vertical nystagmus, minimal vertigo during positional testing, and poor response to repositioning maneuvers. The presence of one or more of these red flags warrants further evaluation. In such cases, high-resolution magnetic resonance imaging of the posterior fossa is strongly recommended to exclude central nervous system lesions.

Patient consent. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of interest. None declared

Author contribution. All authors contributed to the preparation of the manuscript and approved the final version.

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OUR EXPERIENCE IN THE DIAGNOSIS AND MANAGEMENT OF PSYCHOCUTANEOUS DISORDERS IN A TERTIARY CARE CENTER IN ALBANIA.

Migena Vargu[1,2], Sabina Dedej[1], Eriselda Kurushi[2,3], Anxhela Nisi[1], Samuele Vargu[2], Petrit Vargu[2]

[1]Department of Dermatology, University Hospital Center "Mother Teresa", Tirana, Albania
[2]Faculty of Medicine, University of Medicine, Tirana, Albania
[3]Department of Pathology, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding Email: mvargu@yahoo.com

ABSTRACT

Background: Psychocutaneous disorders represent a complex interaction between dermatology and psychiatry and often pose significant diagnostic and therapeutic challenges. Increasing evidence from psychoneuroimmunology has strengthened the understanding of the bidirectional relationship between the skin and the psyche. Dermatologists are frequently the first physicians consulted by these patients, making early recognition and multidisciplinary management essential.

Case Presentation: We present a case series of seven patients diagnosed with primary psychocutaneous disorders, including dermatitis artifacts, delusional parasitosis, neurotic excoriations, and trichotillomania. All patients initially presented to a tertiary dermatology unit with atypical or treatment-resistant cutaneous lesions. Clinical evaluation, laboratory investigations, histopathological examination when indicated, and psychiatric consultation were performed in all cases. Several patients demonstrated significant psychosocial stressors, delayed diagnosis, reluctance to accept psychiatric referrals, and repeated unsuccessful dermatologic treatments before definitive evaluation. Management included a multidisciplinary approach combining dermatologic therapy, psychiatric assessment, psychopharmacologic treatment, and supportive care.

Conclusions: Psychocutaneous disorders remain underrecognized in daily dermatologic practice and may mimic a wide spectrum of dermatologic diseases. Early identification, avoidance of unnecessary investigations, supportive physician-patient communication, and close collaboration between dermatologists and psychiatrists are essential for improving patient outcomes and quality of life. Increased awareness and education in psychodermatology may facilitate earlier diagnosis and more appropriate management of these complex patients.

Keywords: psychodermatology, psychocutaneous disorders, self-inflicted dermatoses, delusional parasitosis, trichotillomania, multidisciplinary management.

EKSPERIENCA JONË NË DIAGNOSTIKIMIN DHE MENAXHIMIN E ÇRREGULLIMEVE PSIKOKUTANE NË NJË QENDËR TERCIARE NË SHQIPËRI

ABSTRAKT

Hyrje: Çrregullimet psikokutane përfaqësojnë një ndërveprim kompleks midis dermatologjisë dhe psikiatrisë dhe shpesh paraqesin sfida të rëndësishme diagnostike dhe terapeutike. Evidencat në rritje nga psiko-neuro-imunologjia kanë forcuar kuptimin e lidhjes dy-drejtimëshe midis lëkurës dhe psikikës. Dermatologët shpesh janë mjekët e parë që konsultohen nga këta pacientë, duke e bërë thelbësore njohjen e hershme dhe menaxhimin multidisiplinar.

Paraqitja e rasteve: Ne paraqesim një seri rastesh me shtatë pacientë të diagnostikuar me çrregullime primare psikokutane, përfshirë dermatit artefakt, parasitozë deluzionale, ekskorime neurotike dhe trikotilomani. Të gjithë pacientët u paraqitën fillimisht në një njësi dermatologjike terciare me lezione kutane atipike ose rezistente ndaj trajtimit. U kryen vlerësim klinik, analiza laboratorike, ekzaminim histopatologjik kur ishte i nevojshëm dhe konsultë psikiatrike në të gjitha rastet. Disa pacientë shfaqën stresorë të rëndësishëm psikosocialë, diagnozë të vonuar, hezitim për të pranuar referimin psikiatrik dhe trajtime të përsëritura dermatologjike të pasuksesshme para vlerësimit përfundimtar. Menaxhimi përfshiu një qasje multidisiplinare që kombinoi trajtimin dermatologjik, vlerësimin psikiatrik, trajtimin psikofarmakologjik dhe kujdesin mbështetës.

Përfundime: Çrregullimet psikokutane mbeten të nënvlerësuara në praktikën e përditshme dermatologjike dhe mund të imitojnë një spektër të gjerë dermatozash. Identifikimi i hershëm, shmangia e ekzaminimeve të panevojshme, komunikimi mbështetës mjek-pacient dhe bashkëpunimi i ngushtë midis dermatologëve dhe psikiatërve janë thelbësore për përmirësimin e rezultateve dhe cilësisë së jetës së pacientëve. Rritja e ndërgjegjësimit dhe edukimit në psikodermatologji mund të lehtësojë diagnozën e hershme dhe menaxhimin më të përshtatshëm të këtyre pacientëve kompleksë.

Fjalë kyçe: psikodermatologji, çrregullime psikokutane, dermatoza të vetë-shkaktuara, parasitozë deluzionale, trikotilomani, menaxhim multidisiplinar

INTRODUCTION

Psychodermatology represents the interface between dermatology and psychiatry and encompasses the interaction between the skin and the mind (1). Both the skin and the central nervous system originate from the embryonic ectoderm, which partially explains their close biological relationship (1,2). Recent advances in psychoneuroimmunology have demonstrated that psychological stress, immune dysregulation, and neuroendocrine alterations contribute significantly to the pathogenesis of several dermatologic conditions (3).

Psychiatric comorbidities are estimated to affect approximately 30-40% of dermatology outpatients, highlighting the importance of psychological assessment in dermatologic practice. Despite this high prevalence, psychocutaneous disorders remain underdiagnosed and

are frequently associated with delayed recognition, repeated consultations, unnecessary investigations, and significant impairment in quality of life (4,5).
Many studies have demonstrated substantial knowledge gaps among dermatologists in recognizing and managing psychocutaneous disorders (6,7). During recent years, our department has devoted greater attention to the multidisciplinary evaluation of these patients. In this article, we present seven cases of psychocutaneous disorders managed in a tertiary dermatology center in Albania and discuss the diagnostic and therapeutic challenges encountered in routine clinical practice.

MATERIALS AND METHODS

This case series includes seven patients who were initially presented to the dermatology department of a tertiary care center. A detailed dermatologic examination was performed in all patients, followed by appropriate laboratory investigations, imaging studies, histopathological examination when indicated, and psychiatric consultation. Clinical, psychological, and social factors associated with disease presentation and management were evaluated retrospectively.

Case 1

A 73-year-old male presented to the dermatology clinic accompanied by his daughter because of multiple painful ulcerative lesions involving the scalp, trunk, and extremities associated with burning sensation and severe pruritus. Symptoms had begun approximately 18 months earlier and reportedly worsened after the diagnosis and subsequent death of his wife from malignancy. The patient was living alone. Dermatologic examination revealed multiple round-to-oval ulcerations with sharply demarcated borders, clean bases, surrounding erythema, excoriations, scars, and post-inflammatory hyperpigmentation. The lesions were distributed in atypical, easily accessible areas (Fig. 1, 2). Laboratory and imaging investigations were unremarkable. Bacteriological culture revealed Escherichia coli, while histopathologic examination showed nonspecific findings. During psychiatric evaluation, the patient reported severe insomnia with only 3-4 hours of sleep per night. Detailed anamnesis ultimately revealed self-inflicted lesions caused by burning the skin with matches, partially admitted after persistent psychiatric interviewing. Treatment included escitalopram 20 mg daily, lorazepam 1.25 mg at night, topical wound care, and antibacterial therapy.



Figure 1. Case 1- Bizarre ulcerations of varying sizes on the arm.



Figure 2. Case 1- Multiple scars and ulcerations on the back.

Case 2

A 68-year-old female presented with generalized pruritus involving the scalp, face, and body associated with insomnia for approximately six months. She reported that symptoms began after an insect bite near the right eyebrow and described a persistent sensation of living organisms moving beneath the skin (Fig.3). Medical history included hypertension, cardiac arrhythmia, and varicose veins. Dermatologic examination demonstrated only a few erythematous papules with mild scaling. Laboratory and imaging studies were normal. Psychiatric consultation suggested a somatic-type delusional disorder consistent with delusional parasitosis. Treatment with fluvoxamine 100 mg daily and lorazepam was initiated.



Figure 3. Case 2- Erythematous papules below the right eyebrow (red arrow)

Case 3

A 10-year-old girl presented with severe generalized pruritus predominantly affecting the trunk and extremities for six months, with nocturnal exacerbation. Dermatologic examination revealed multiple bilateral papulonodular lesions with central erosions, excoriations, and post-inflammatory hyperpigmentation (Fig.4). Laboratory investigations, imaging studies, and skin biopsy were nonspecific. Psychiatric evaluation identified anxiety symptoms and compulsive behaviors associated with excessive fear of microbes and disease contamination. Short-term treatment with phenibut 250 mg was recommended, together with psychological follow-up.



Figure 4. Case 3- Hyperpigmented nodules with fine central scaling on the leg.

Case 4

A 63-year-old woman presented with pruritic papular lesions involving the chest and upper extremities associated with intense scalp pruritus. She reported chronic insomnia and had been living alone since the death of her husband six years earlier. Dermatologic examination demonstrated brownish-red papules with superficial erosions, serohemorrhagic crusts, and post-inflammatory hyperpigmentation (Fig.5). Histopathologic examination revealed chronic eczema with marked ulceration. Based on the clinical presentation and psychiatric assessment, neurotic excoriations were diagnosed. The patient received topical dermatologic therapy and psychiatric follow-up.



Figure 5. Case 4- Hyperpigmentation on the back and some excoriations

Case 5

A female patient presented with ulcerative lesions involving exposed areas of the face and accessible parts of the extremities. The lesions had irregular borders and atypical distribution. She persistently reported parasite infestation and repeatedly manipulated the lesions to remove them (Fig.6). Psychiatric consultation confirmed the diagnosis of delusional parasitosis.



Figure 6. Case 5- Excoriations and ulcerations of the face secondary to repetitive skin picking.

Case 6

A female patient presented with complaints of hair loss and brought tufts of removed hair to the consultation. Neither the patient nor her mother initially accepted a self-induced cause. No pruritus or burning sensation preceded the onset of alopecia. Examination of the scalp revealed a large patch of alopecia involving the vertex, broken hairs of varying lengths, black dots, and otherwise normal scalp skin (Fig.7). Clinical findings were highly suggestive of trichotillomania, and psychiatric follow-up was recommended.

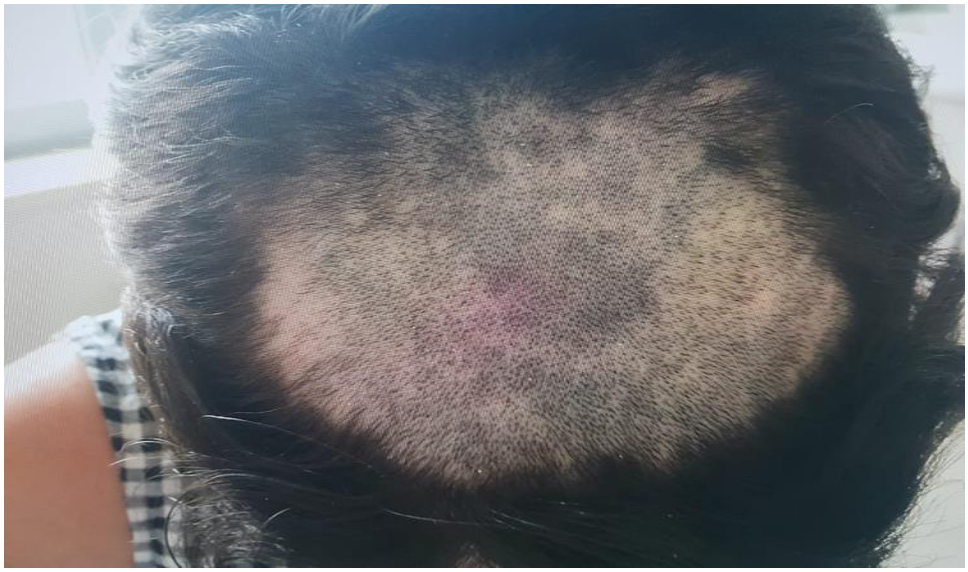


Figure 7. Case 6- A large area of hair loss with shortened and thinned hairs, varying length hairs, and black dots.

Case 7

A male patient presented with small erosive lesions on the scalp that had initially been treated as folliculitis without clinical improvement. Detailed anamnesis revealed significant anxiety symptoms that worsened following the diagnosis of malignancy in his spouse (Fig. 8). Based on clinical history, lesion morphology, and atypical treatment resistance, the lesions were considered self-inflicted. In addition to dermatologic management, psychiatric consultation was strongly recommended.



Figure 8. Case 7- Irregularly distributed erosive scalp lesions.

DISCUSSION

Psychocutaneous disorders represent a clinically significant but often underrecognized group of conditions at the interface of dermatology and psychiatry. In routine dermatologic practice, these patients rarely present with overt psychiatric complaints; instead, they seek care for persistent, treatment-resistant cutaneous symptoms. This clinical pattern is well documented in the literature, where studies show that a substantial proportion of patients with primary psychocutaneous disorders initially undergo multiple dermatologic consultations and even invasive diagnostic procedures before the correct diagnosis is established (8,9). In our case series, all patients first presented to dermatology services, and psychiatric referral was frequently delayed, reflecting a common global diagnostic pathway characterized by underrecognition and fragmentation of care.

A key observation in our cohort was the strong association between psychosocial stressors and disease onset or exacerbation. Bereavement, social isolation, chronic insomnia, and

anxiety-related symptoms were recurrent across several cases, particularly among elderly patients living alone. This finding aligns with psychoneuroimmunology models, which show that chronic psychological stress can alter hypothalamic–pituitary–adrenal axis activity, immune regulation, and neuroinflammatory pathways, thereby influencing both the perception of pruritus and behavior-related skin damage. Large clinical reviews have similarly reported that stressful life events are common in patients with dermatitis artefacta, neurotic excoriations, and trichotillomania, acting as both triggering and perpetuating factors (10, 11). In our series, stress-related vulnerability was particularly prominent in cases 1, 4, and 7, where recent bereavement or severe emotional distress preceded symptom onset or exacerbation.

Another major diagnostic challenge highlighted by our experience is the marked clinical overlap between psychocutaneous disorders and common inflammatory or infectious dermatoses. Patients often present with nonspecific lesions such as erosions, excoriations, nodules, or ulcerations, which mimic prurigo nodularis, chronic eczema, folliculitis, or even infectious processes. As described in prior dermatologic studies, atypical lesion morphology, geometrical or accessible distribution, and discordance between clinical findings and reported symptom severity are important diagnostic clues suggesting a psychogenic origin (12,13). In our cases, repeated negative laboratory results and nonspecific histopathology further contributed to diagnostic uncertainty, often prolonging the time to psychiatric evaluation.

A particularly relevant finding in our series was the high rate of prior misdiagnosis and prolonged ineffective dermatologic treatment before psychocutaneous disorders were considered. This is a well-recognized phenomenon in literature, where patients with dermatitis artefacta or delusional parasitosis may undergo repeated antibiotic therapy, topical corticosteroid use, or even surgical interventions without clinical improvement. Such delays not only increase healthcare utilization but may also reinforce maladaptive illness behavior and reduce patient trust in medical professionals. Jafferany et al. have shown that early recognition and reframing of the diagnosis in a non-confrontational manner significantly improve patient adherence and reduce unnecessary interventions (14).

Communication and the physician–patient relationship emerged as a central determinant of clinical outcome in our series. Many patients initially denied self-inflicted behavior or resisted psychiatric referral, which is consistent with known poor insight in disorders such as delusional parasitosis and trichotillomania. Literature emphasizes that confrontation often leads to therapeutic rupture, whereas a neutral, empathetic, and non-judgmental approach facilitates gradual acceptance of psychiatric involvement (15). In our experience, supportive communication strategies were essential in achieving partial insight and treatment adherence, particularly in cases involving somatic delusions or compulsive behaviors.

The importance of multidisciplinary management was strongly evident across all cases. Combined dermatologic and psychiatric intervention allowed for more accurate diagnosis, reduced unnecessary investigations, and improved therapeutic planning. Current evidence supports integrated psychodermatology models in which cognitive behavioral therapy, selective serotonin reuptake inhibitors, and habit reversal techniques are used alongside dermatologic care. Such integrated approaches have been shown to improve symptom control, reduce relapse rates, and enhance quality of life, particularly in trichotillomania and neurotic excoriations (16,17)

Finally, our case series underscores that psychocutaneous disorders should be actively considered in patients with chronic, atypical, or treatment-resistant dermatoses, especially when lesions are in accessible body areas and when clinical findings do not fully explain symptom severity. Early recognition is critical not only to prevent chronic skin damage but also to reduce psychological distress, social impairment, and healthcare burden. Increasing awareness among dermatologists remains essential, particularly in settings where structured psychodermatology services are still limited.
The main limitation of this report is the small sample size and retrospective descriptive design.

CONCLUSIONS

Our case series highlights the importance of careful clinical observation, detailed psychosocial assessment, recognition of atypical lesion morphology, close collaboration between dermatologists and psychiatrists, and maintenance of a supportive, nonjudgmental physician-patient relationship. Early diagnosis may help avoid unnecessary investigations, prolonged ineffective treatments, repeated consultations, and additional psychological distress. Greater awareness and education in psychodermatology are needed, particularly in countries where this field remains insufficiently recognized in routine clinical practice.
Patient Consent: Written informed consent was obtained from all patients (or their legal guardians) for publication of the clinical data and identifiable clinical images.
Conflict of Interest: The authors declare no conflict of interest.
Author Contributions: All authors contributed to the preparation of the manuscript and approved the final version.

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HEPARIN-INDUCED DELAYED-TYPE HYPERSENSITIVITY REACTION: TWO CASE REPORTS AND MANAGEMENT STRATEGIES

Mehmet Hoxha[1,2], Ester Ndreu[2]

[1] Faculty of Medicine, University of Medicine, Tirana, Albania
[2] University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding E-mail: esterndreu3@gmail.com

ABSTRACT

Background: Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is a rare but clinically significant adverse effect of low molecular weight heparins (LMWHs). It represents a type IV hypersensitivity reaction mediated by T lymphocytes and typically occurs 1-3 weeks after treatment initiation. Clinically, it presents with pruritic erythematous plaques at injection sites, sometimes spreading beyond. Early recognition is essential to avoid complications and to ensure safe anticoagulant substitution**.**
Case Report: We report two cases of HIDHR in different clinical settings. The first case involves a 30-year-old pregnant woman in her first trimester receiving enoxaparin for thromboprophylaxis who developed pruritic erythematous plaques at injection sites that subsequently spread to the trunk after three weeks of therapy. Platelet count remained normal. Enoxaparin was discontinued and replaced with unfractionated heparin, leading to complete resolution of lesions within 10 days. The second case describes a 65-year-old woman after total abdominal hysterectomy who was treated with fraxiparine and developed similar lesions after three weeks. The drug was discontinued and replaced with fondaparinux, resulting in complete resolution within two weeks. Patch testing confirmed the diagnosis in the second case, while the first diagnosis was based on clinical and histopathological findings.
Conclusion: HIDHR is an uncommon but important complication of LMWH therapy, with consistent immunologic mechanisms across different clinical contexts. Early discontinuation of the offending agent and substitution with alternatives such as unfractionated heparin or fondaparinux ensures safe and effective anticoagulation. Awareness of this condition and potential cross-reactivity among LMWHs is essential for optimal patient management.

Keywords: Heparin-induced delayed-type hypersensitivity reaction; Low-Molecular-Weight Heparin; Drug Hypersensitivity; Enoxaparin; Fondaparinux.

REAKSION HIPERSENSITIV I TIPIT TË VONUAR I INDUKTUAR NGA HEPARINA: DY RASTE KLINIKE DHE STRATEGJITË E MENAXHIMIT

ABSTRAKT

Hyrje: Reaksioni i vonuar i hipersensibilitetit i induktuar nga heparina (HIDHR) është një efekt anësor i rrallë por klinikisht i rëndësishëm i heparinave me peshë molekulare të ulët

(LMWH). Ai përfaqëson një reaksion të tipit IV të ndërmjetësuar nga limfocitet T dhe zakonisht shfaqet 1–3 javë pas fillimit të trajtimit, me pllaka eritematoze dhe prurit në vendin e injeksionit. Njohja e hershme është thelbësore për të shmangur komplikacionet dhe për të zgjedhur një alternativë të sigurt antikoagulante.

Prezantimi rasteve: Paraqesim dy raste me HIDHR në kontekste të ndryshme klinike. Rasti i parë është një grua 30-vjeçare në tremujorin e parë të shtatzënisë, e trajtuar me enoksaparinë për tromboprofilaksi, e cila zhvilloi pllaka eritematoze me kruarje në vendet e injeksionit, me përhapje në trung pas tre javësh trajtimi. Numri i trombociteve ishte normal. Terapia u ndërpre dhe u zëvendësua me heparinë të pafraksionuar, me përmirësim të plotë të lezioneve brenda 10 ditësh. Rasti i dytë është një grua 65-vjeçare pas histerektomie abdominale totale, në trajtim me fraxiparinë, e cila zhvilloi manifestime të ngjashme pas tre javësh. Medikamenti u ndërpre dhe u zëvendësua me fondaparinuks, duke çuar në rezolucion të plotë të lezioneve brenda dy javësh. Në rastin e dytë, "patch" testi konfirmoi diagnozën, ndërsa në rastin e parë diagnoza u bazua në gjetjet klinike dhe histopatologjike.

Përfundime: HIDHR është një komplikacion i rrallë por i rëndësishëm i LMWH-ve me një mekanizëm imunologjik të përbashkët në kontekste të ndryshme klinike. Ndërprerja e hershme e medikamentit shkaktar dhe zëvendësimi me alternativa si heparina e pafraksionuar ose fondaparinuksi sigurojnë një trajtim të sigurt dhe efektiv. Rritja e ndërgjegjësimit për këtë gjendje dhe për mundësinë e reaksioneve të kryqëzuara është thelbësore për menaxhim optimal.

Fjalë kyç: Reaksioni i mbindjeshmërisë së vonuar i induktuar nga heparina; Heparina me peshë molekulare të ulët; Mbindjeshmëria ndaj barnave; Enoksaparina; Fondaparinuks.

INTRODUCTION

Low molecular weight heparins (LMWHs) are widely used anticoagulants in clinical practice, particularly in pregnancy and perioperative settings, due to their predictable pharmacokinetics, ease of administration, and lower risk of heparin-induced thrombocytopenia compared to unfractionated heparin (UFH) [1,2]. Despite their favorable safety profile, LMWHs may be associated with rare adverse effects, including delayed-type hypersensitivity reactions Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is an uncommon cutaneous adverse reaction mediated by T lymphocytes and classified as a type IV hypersensitivity reaction [2,6]. It typically occurs 1–3 weeks after initiation of therapy and presents as pruritic erythematous plaques at injection sites, which may occasionally generalize [5]. Histopathological findings usually reveal perivascular lymphocytic infiltrates with eosinophils, supporting an immune-mediated mechanism [6].The pathogenesis of HIDHR involves the role of LMWHs as haptens that bind to endogenous proteins, leading to sensitization and subsequent immune activation upon repeated exposure [6]. An important clinical challenge is the high rate of cross-reactivity among different LMWHs, reported in more than 50% of cases, which limits therapeutic alternatives [7]. Consequently, switching between LMWHs is not generally recommended. Early recognition of HIDHR is essential to avoid progression of skin lesions and to ensure safe continuation of

anticoagulation therapy. Alternative anticoagulants such as UFH or fondaparinux are often used depending on the clinical context, including pregnancy status [1,5,7].In this report, we present two cases of HIDHR occurring in different clinical settings, highlighting their similar clinical presentation and underlying immunologic mechanisms, as well as management strategies.

CASE PRESENTATION

A 30-year-old woman in the first trimester of pregnancy was started on enoxaparin 40 mg once daily for thromboprophylaxis due to increased thrombotic risk in pregnancy. After three weeks of treatment, she developed pruritic, erythematous plaques at the injection sites on the abdomen, with subsequent spread to the trunk. Cutaneous lesions are shown in Figure 1. There were no systemic symptoms. Laboratory findings showed a normal platelet count and no eosinophilia.

Dermatology consultation was performed, and a skin biopsy revealed perivascular lymphocytic infiltrates with eosinophils, consistent with a delayed-type hypersensitivity reaction. Based on clinical and histopathological findings, HIDHR was diagnosed. Enoxaparin was discontinued and replaced with unfractionated heparin. Treatment with topical corticosteroids and oral antihistamines led to complete resolution within 10 days.

Patch testing was not performed during pregnancy due to safety considerations and was not completed postpartum due to limited follow-up.



Figure 1. Erythematous pruritic plaques at enoxaparin injection sites in Case 1.

Case 2

A 65-year-old woman underwent total abdominal hysterectomy and received fraxiparine 0.4 mL (3800 IU anti-Xa) once daily for postoperative thromboprophylaxis. After approximately three weeks, she developed pruritic erythematous plaques at the injection sites, extending to the trunk (Fig. 2). No systemic symptoms were present. Laboratory evaluation showed a normal platelet count and mild eosinophilia.

A dermatology consultation was obtained, and a skin biopsy demonstrated perivascular lymphocytic infiltration with eosinophils, supporting a diagnosis of delayed-type hypersensitivity. Fraxiparine was discontinued and replaced with fondaparinux.

Topical corticosteroid therapy resulted in complete resolution of lesions within two weeks. Patch testing performed four months later was positive for fraxiparine and negative for fondaparinux.



Figure 2. Cutaneous lesions associated with fraxiparine-induced delayed hypersensitivity in Case 2.

DISCUSSION

HIDHR is a rare but clinically relevant adverse reaction to LMWHs, mediated by a delayed-type (type IV) hypersensitivity mechanism involving sensitized T lymphocytes [1,3,6]. The characteristic onset 1–3 weeks after initiation of therapy reflects the time required for immune sensitization and subsequent elicitation upon repeated exposure [6].

Clinically, HIDHR typically presents with pruritic erythematous plaques at injection sites, which may extend beyond these areas, as observed in both of our patients [2,6]. The absence of thrombocytopenia helps distinguish HIDHR from heparin-induced thrombocytopenia, a potentially life-threatening immune-mediated complication [3]. In our cases, normal platelet counts supported the diagnosis of a localized cutaneous hypersensitivity reaction rather than HIT.

The differential diagnosis also includes cellulitis and other cutaneous drug reactions. Cellulitis is usually associated with localized pain, warmth, and systemic signs such as fever, and typically lacks the characteristic delayed onset and pruritus seen in HIDHR. Other injection-site reactions, including irritative or immediate hypersensitivity responses, tend to occur earlier after drug administration and are not mediated by a delayed T-cell response. In contrast, the timing, morphology, and histopathological findings in our patients were consistent with HIDHR.

The underlying pathophysiology involves LMWH molecules acting as haptens that bind to endogenous proteins, forming antigenic complexes that activate T cells [2,6]. Histological findings described in the literature include perivascular lymphocytic infiltrates with eosinophils, consistent with a delayed hypersensitivity response [6].

Management of HIDHR requires prompt discontinuation of the offending agent. Supportive treatment with topical corticosteroids and antihistamines is usually sufficient, while systemic corticosteroids are rarely needed [2,5]. Both patients in our report showed rapid clinical improvement following drug withdrawal and symptomatic therapy.

A major therapeutic challenge is the high rate of cross-reactivity among LMWHs, reported in more than half of cases [2,7]. For this reason, switching from one LMWH to another is generally discouraged. Instead, alternative anticoagulants should be considered based on patient-specific factors.

In pregnant patients, UFH is often the preferred alternative due to its safety and minimal cross-reactivity, as demonstrated in our first case [1,5]. In non-pregnant patients, fondaparinux represents an effective and well-tolerated option, with a low incidence of cross-reactivity [5]. Our second case supports this approach, as the patient tolerated fondaparinux without recurrence of symptoms.

Patch testing is a valuable tool for confirming delayed-type hypersensitivity to heparins and for assessing potential cross-reactivity [6]. However, it is not always feasible during the acute phase, particularly in pregnant patients, where it is often deferred due to safety and practical considerations. In our report, patch testing was performed only in the second case and supported the diagnosis. In contrast, in the first case, the diagnosis was based on clinical presentation and response to drug withdrawal. Although helpful, patch testing is not essential when clinical features and temporal association are typical.

The prognosis of HIDHR is excellent once the causative agent is discontinued, with most lesions resolving within one to two weeks [6]. However, failure to recognize this condition may lead to unnecessary continuation of the offending drug and worsening of symptoms.

Table 1. Recommended Anticoagulant Alternatives

Anticoagulant	**Pregnancy Safety**	**Cross-Reactivity**	**Comment**
Enoxaparin (LMWH)	Safe	High	First-line, may trigger HIDHR
Dalteparin (LMWH)	Safe	High	Similar to enoxaparin
UFH	Safe	Low	Preferred in pregnancy after HIDHR
Fondaparinux	Caution	Rare	Good alternative in non-pregnant patients
Warfarin	Contraindicated	N/A	Teratogenic

LIMITATIONS

This report has two main limitations. First, patch testing was not performed during pregnancy in one case due to safety and practical considerations, thereby delaying immunologic confirmation. Secondly, as a small case series, the findings may not be generalizable but provide clinically relevant insights into the recognition and management of HIDHR.

CONCLUSION

Heparin-induced delayed-type hypersensitivity reaction (HIDHR) is a rare but important complication of LMWH therapy. Early recognition and prompt discontinuation of the offending agent are essential for rapid resolution. Due to frequent cross-reactivity among LMWHs, alternative anticoagulants such as unfractionated heparin or fondaparinux should be considered. Increased clinical awareness is key to ensuring safe and effective management.

Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: All authors contributed to the preparation of the manuscript and approved the final version.

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CASE REPORT

NODULAR LESIONS IN AN ELDERLY PATIENT REVEALED BY DERMOSCOPY.

Migena Vargu[1,2], Sabina Dedej[1], Eriselda Kurushi[2,3], Anxhela Nisi[1], Samuele Vargu[2], Petrit Vargu[2]

[1]Service of Dermatology, University Hospital Center "Mother Teresa", Tirana, Albania

[2]Faculty of Medicine, University of Medicine of Tirana, Tirana, Albania

[3]Department of Pathology, University Hospital Center "Mother Teresa", Tirana, Albania

Corresponding Email: mvargu@yahoo.com

ABSTRACT

Background: Kaposi sarcoma (KS) is a vascular neoplasm associated with infection by Human Herpesvirus-8 (HHV-8). Although classical KS typically affects elderly men of Mediterranean or Eastern European origin, its clinical presentation may mimic a variety of benign and malignant vascular tumors, posing diagnostic challenges. Dermoscopy has emerged as a valuable noninvasive tool, particularly for identifying the characteristic rainbow pattern.

Case Presentation: A 72-year-old Caucasian man presented with two slowly enlarging nodules located on the upper and lower extremities. The lesions had progressively increased in size over several months and were asymptomatic. The patient had a history of diabetes mellitus and no history of recent travel or animal exposure. Laboratory investigations were unremarkable, and HIV serology was negative. Imaging studies, including whole-body computed tomography and ultrasonography, excluded lymphadenopathy and internal malignancies. Dermoscopic examination revealed a polychromatic rainbow pattern. Histopathological evaluation demonstrated spindle-cell proliferation with slit-like vascular spaces containing erythrocytes. Immunohistochemical staining showed positivity for CD34, D2-40, and HHV-8, confirming the diagnosis of Kaposi sarcoma. Given the localized disease, radiotherapy was selected as the treatment of choice.

Conclusions: Through this case, we discuss the importance of integrating dermoscopy, histopathology, and immunohistochemistry in diagnosing Kaposi sarcoma. Recognition of the rainbow pattern may facilitate early diagnostic suspicion and prompt confirmation with biopsy.

Keywords: Kaposi sarcoma, dermoscopy, rainbow pattern, HHV-8, immunohistochemistry, radiotherapy.

LEZIONET NODULARE NË NJË PACIENT TË MOSHUAR TË ZBULUAR ME DERMATOSKOPI

ABSTRAKT

Hyrje: Sarkoma e Kaposit (SK) është një neoplazi vaskulare e lidhur me infeksionin nga Human Herpesvirus-8 (HHV-8). Megjithëse forma klasike e SK prek zakonisht meshkuj të moshuar me origjinë mesdhetare ose të Evropës Lindore, paraqitja klinike e saj mund të ngjasojë me tumore të ndryshme vaskulare beninje dhe malinje, duke paraqitur sfida diagnostike. Dermoskopia është shfaqur si një mjet i vlefshëm jo invaziv, veçanërisht përmes identifikimit të modelit karakteristik të ylbertë (rainbow pattern).

Paraqitja e rastit: Një burrë kaukazian 72-vjeçar u paraqit me dy noduse me rritje të ngadaltë, të lokalizuara në ekstremitetet e sipërme dhe të poshtme. Lezionet ishin rritur progresivisht në përmasa gjatë disa muajve dhe ishin asimptomatike. Pacienti kishte histori të diabetit mellitus dhe nuk raportonte udhëtime të fundit apo ekspozim ndaj kafshëve. Ekzaminimet laboratorike rezultuan pa gjetje të veçanta dhe serologjia për HIV ishte negative. Ekzaminimet imazherike, përfshirë tomografinë e kompjuterizuar të të gjithë trupit dhe ultrasonografinë, përjashtuan praninë e limfadenopative dhe maligniteteve të brendshme. Ekzaminimi dermoskopik zbuloi një model polikromatik të tipit rainbow pattern. Vlerësimi histopatologjik tregoi proliferim të qelizave fusiforme me hapësira vaskulare në formë çarjesh që përmbanin eritrocite. Ngjyrosja imunohistokimike rezultoi pozitive për CD34, D2-40 dhe HHV-8, duke konfirmuar diagnozën e sarkomës Kaposi. Duke qenë se sëmundja ishte e lokalizuar, radioterapia u zgjodh si trajtimi i preferuar.

Përfundime: Nëpërmjet këtij rasti, diskutojmë rëndësinë e integrimit të dermoskopisë, histopatologjisë dhe imunohistokimisë në diagnostikimin e sarkomës Kaposi. Njohja e modelit rainbow pattern mund të lehtësojë ngritjen e hershme të dyshimit diagnostik dhe të mundësojë konfirmimin e shpejtë përmes biopsisë.

Fjalë kyçe: Sarkoma Kaposi, dermoskopia, modeli ylber (rainbow pattern), HHV-8, imunohistokimia, radioterapia.

INTRODUCTION

Kaposi sarcoma (KS) is a multifocal angioproliferative neoplasm linked to Human Herpesvirus-8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (1). It was first described in 1872 by the Hungarian dermatologist Moritz Kaposi as a multifocal pigmented skin sarcoma affecting elderly European men (2). Four epidemiological variants have been described: classical, endemic African, iatrogenic, and epidemic (HIV-associated) KS. Classical KS typically presents as slowly progressive violaceous macules, plaques, or nodules involving the lower extremities (1-3).

The incidence of classical KS varies geographically. Before the HIV/AIDS epidemic, KS was a rare cancer, with incidence rates ranging from 0.01 per 100,000 person-years in the United Kingdom to 1.6 per 100,000 person-years in Sardinia, and it occurred 2–3 times more frequently in men than in women. Recent international data reported KS incidence rates of 280 per 100,000 person-years in South Africa, 244 per 100,000 in Latin America, 237 per

100,000 in North America, 180 per 100,000 in Europe, and 52 per 100,000 in the Asia-Pacific region. HHV-8 infection is considered necessary, although not sufficient, for tumor development. Additional factors, including immune dysregulation, aging, and chronic inflammation, contribute to disease pathogenesis (1,3,4).

The diagnosis of KS may be challenging because its clinical appearance overlaps with several vascular and spindle-cell neoplasms. Dermoscopy has become increasingly useful in daily dermatologic practice. Among the dermoscopic features reported, the rainbow pattern has attracted particular attention and histologically is correlated with the presence of hyaline globules (5). Cheng et al. reported that this multicolored appearance is one of the most characteristic dermoscopic findings of KS and may serve as an important clue prompting histopathological confirmation (6).

We report a case of nodular Kaposi sarcoma in an elderly patient in whom dermoscopy, histopathology, and immunohistochemistry played complementary roles in establishing the diagnosis.

CASE PRESENTATION

A 72-year-old Caucasian male was referred to our dermatology department for evaluation of two slowly growing nodules located on the upper and lower extremities (Fig. 1).

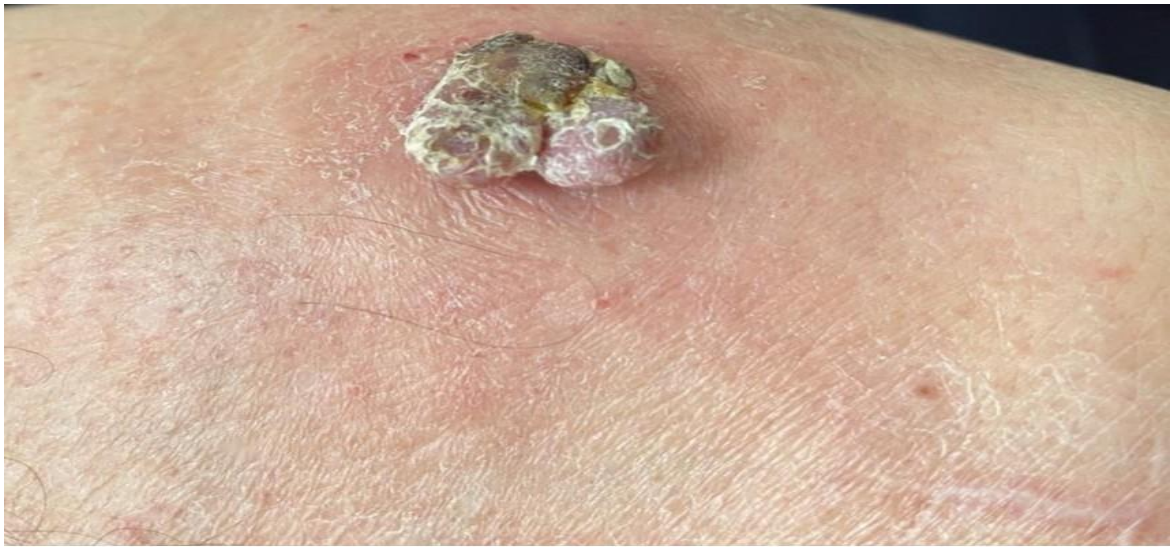


Figure 1. Clinical picture of the nodular lesion located in the forearm.

According to the patient, the lesions gradually enlarged over several months without pain, pruritus, bleeding, or ulceration. His medical history was significant for type 2 diabetes mellitus. He denied recent travel, animal contact, immunosuppressive therapy, or prior malignancies. Physical examination revealed two well-defined, skin-colored nodules. No mucosal lesions or palpable lymphadenopathy were noted.

Laboratory investigations, including routine hematologic and biochemical analyses, showed no significant abnormalities. HIV serology was negative. Whole-body computed tomography and ultrasonography revealed no lymph node enlargement or visceral involvement. Dermoscopic examination under polarized light showed a polychromatic appearance with a rainbow pattern (Fig. 2), along with whitish structures and vascular features.

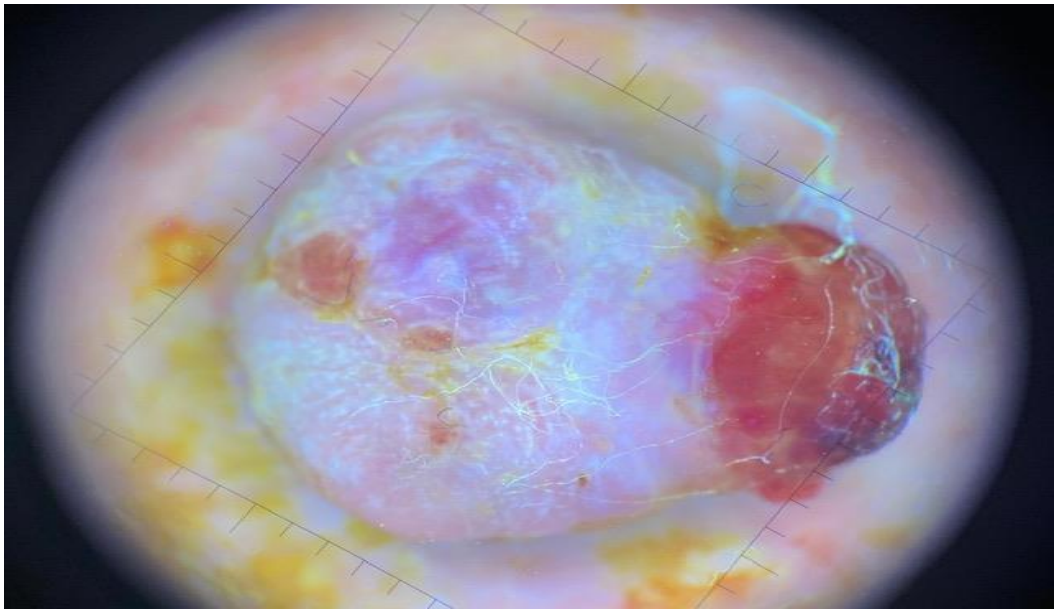


Figure 2. Dermoscopy of the nodular Kaposi sarcoma with a rainbow pattern.

A skin biopsy was performed. Histopathological examination revealed a nodular proliferation of spindle-shaped cells arranged in fascicles, associated with slit-like vascular spaces containing erythrocytes and a mixed inflammatory infiltrate. Immunohistochemical analysis demonstrated positivity for CD34, D2-40, and HHV-8 (Fig. 3), confirming the diagnosis of Kaposi sarcoma.



Figure 3. Histopathology. A) H&E staining showing the lobular architecture. B) Immunohistochemistry positive for CD34. C) Immunohistochemistry positive for HHV-8.

Considering the localized nature of the disease, the absence of visceral involvement, and the limited number of lesions, radiotherapy was selected as the preferred therapeutic approach. This decision was based on the well-established radiosensitivity of localized KS and the excellent cosmetic and therapeutic outcomes reported in the literature.

DISCUSSION

Kaposi sarcoma (KS) is a low-grade vascular neoplasm characterized by endothelial and spindle-cell proliferation driven by infection with Human Herpesvirus-8 (HHV-8). Since its first description, the disease has evolved from being considered a rare dermatologic entity to a well-recognized vascular tumor with distinct epidemiological variants. Although HIV-associated KS remains the most prevalent form worldwide, classical KS continues to represent an important diagnostic consideration in elderly individuals, particularly in Mediterranean and Eastern European populations (1,3,7).

The patient described in our report aligns with the demographic profile of classical Kaposi sarcoma, presenting as an elderly male with slowly progressive nodular lesions and no evidence of HIV infection or systemic immunosuppression. Classical KS typically follows an indolent clinical course and predominantly affects the lower extremities; however, lesions may also occur at other anatomical sites, as observed in our patient. Because the clinical presentation can be highly variable, a diagnosis based solely on visual inspection may be challenging.

The pathogenesis of KS is complex and multifactorial. HHV-8 infection is considered a necessary prerequisite for disease development, yet only a minority of infected individuals develop tumors (8). Cesarman et al. reported that HHV-8 promotes oncogenesis by interacting with host pathways that regulate angiogenesis, inflammation, apoptosis, and cell proliferation. Viral proteins stimulate the production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-6, and other proangiogenic mediators, leading to the characteristic vascular proliferation observed in KS lesions (1). In classical KS, age-related immune dysregulation may further contribute to disease development by facilitating viral persistence and endothelial transformation (4).

One of the most notable features of the present case is its dermoscopic appearance. Dermoscopy has become an indispensable diagnostic tool in modern dermatology and increasingly plays a role in assessing vascular tumors (9). Among the dermoscopic features described in Kaposi sarcoma, the rainbow pattern is considered one of the most characteristic findings. Under polarized dermoscopy, it appears as multiple colors forming a polychromatic structure (5,6). Initially thought to be pathognomonic of KS, subsequent studies have shown that rainbow patterns may be observed in other vascular and hemorrhagic lesions (10). Nevertheless, the presence of this feature should raise strong suspicion for Kaposi sarcoma, especially in the appropriate clinical context (5,6,9,10). The optical basis of the rainbow pattern remains incompletely understood. Current theories suggest that it results from diffraction and polarization of light within densely packed vascular channels and spindle-cell bundles. Extravasated erythrocytes may further contribute to this appearance (11). In our patient, identification of a rainbow pattern significantly narrowed the differential diagnosis and prompted histopathological confirmation.

The differential diagnosis of nodular Kaposi sarcoma is broad and includes both benign and malignant conditions. Bacillary angiomatosis is a major clinical mimic, particularly in immunocompromised patients. Both diseases may present as violaceous papules and nodules; however, bacillary angiomatosis typically shows lobular capillary proliferation with prominent neutrophilic inflammation and Bartonella organisms detectable with special stains

(12). Pyogenic granuloma may resemble nodular KS because of its vascular appearance and reddish coloration. Unlike KS, pyogenic granuloma typically grows rapidly, bleeds easily, and histologically exhibits a lobular capillary architecture without spindle cells or HHV-8 expression (9). Angiosarcoma shares the vascular nature and violaceous appearance of KS but is generally more aggressive. Histologically, angiosarcoma shows marked cellular atypia, pleomorphism, and numerous mitoses, features that are absent or minimal in KS. Furthermore, angiosarcoma is HHV-8 negative (9). Dermatofibrosarcoma protuberans (DFSP) can present as a slowly enlarging nodular lesion similar to KS. However, DFSP is characterized by a storiform spindle-cell proliferation infiltrating the subcutaneous fat and lacks the vascular spaces and HHV-8 positivity typical of KS (13). Merkel cell carcinoma may clinically resemble nodular KS in elderly patients. However, it expresses CK20 and neuroendocrine markers, whereas KS demonstrates vascular differentiation and HHV-8 positivity (13). Rosai-Dorfman disease may occasionally manifest as cutaneous nodules, but it is distinguished by large S100-positive histiocytes showing emperipolesis, a feature not seen in KS (14). Pseudo-Kaposi sarcoma (acrocangiodermatitis) may present with violaceous plaques or nodules on the lower extremities. However, pseudo-Kaposi sarcoma is a reactive vascular proliferation associated with venous insufficiency and lacks HHV-8 positivity and true spindle-cell neoplastic proliferation (15).

Histopathology remains the gold standard for diagnosis. The characteristic microscopic features of KS include spindle-cell proliferation, slit-like vascular spaces, erythrocyte extravasation, hemosiderin deposition, and inflammatory infiltrates rich in plasma cells. However, histological overlap with other vascular neoplasms occasionally necessitates immunohistochemical confirmation. HHV-8 latent nuclear antigen-1 (LNA-1) staining is considered the most specific diagnostic marker and has significantly improved diagnostic accuracy in recent decades. Positive HHV-8 staining, together with expression of vascular markers such as CD34 and D2-40, established the diagnosis in our patient and effectively excluded alternative spindle-cell tumors (1,16).

An additional strength of this case is its multimodal diagnostic approach, combining clinical examination, dermoscopy, histopathology, and immunohistochemistry. Increasing evidence supports using dermoscopy as an intermediate step between clinical suspicion and tissue diagnosis, enabling clinicians to identify lesions that warrant biopsy and facilitating earlier diagnosis. In daily practice, recognizing dermoscopic clues, such as the rainbow pattern, may shorten diagnostic delay and reduce the likelihood of misclassification as benign vascular lesions.

A staging system for classical Kaposi sarcoma was proposed in 2003, classifying disease into four stages (macular–nodular, infiltrative, florid, and disseminated). However, this classification has not been prospectively validated; therefore, there is no specific prognostic staging system for classical KS (17). Treatment selection in Kaposi sarcoma depends on disease subtype, number of lesions, anatomical distribution, symptoms, cosmetic concerns, and systemic involvement. Localized disease can often be managed successfully with local therapies, including surgical excision, intralesional chemotherapy, or radiotherapy. In contrast, disseminated disease may require systemic treatment such as liposomal doxorubicin, paclitaxel, interferon-alpha, or targeted therapies (18). Radiotherapy was chosen for our patient because the lesions were localized and there was no evidence of visceral disease.

Kaposi sarcoma is highly radiosensitive, and radiotherapy has consistently demonstrated excellent response rates. Several studies have reported local control rates of 80%-90%, with significant symptomatic improvement and favorable cosmetic outcomes. Radiotherapy avoids surgical morbidity and is particularly suitable for elderly patients or cosmetically sensitive areas. The literature supports doses of 20 to 30 Gy for localized disease, providing durable tumor control while minimizing adverse effects (18-20).

CONCLUSIONS

The identification of a rainbow pattern in a nodular lesion should prompt consideration of Kaposi sarcoma. Although not entirely specific, this dermoscopic finding may represent an important diagnostic clue when interpreted in the appropriate clinical context. For localized disease, radiotherapy represents a highly effective therapeutic option, offering excellent local control and favorable cosmetic outcomes. Early recognition and multidisciplinary evaluation remain essential for optimal patient management.

Patient Consent: Written informed consent was obtained from the patient (or his legal guardians) for publication of the clinical data and identifiable clinical images.

Conflict of Interest: The authors declare no conflict of interest.

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