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Contact number : +355 694040521

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GREETING SPEECH

Dear colleagues, partners, friends and future readers of the Albanian Journal of Internal Medicine,

On behalf of all the contributors to this new Journal, I would like to express our understanding of the significant responsibility we are undertaking with the publication of this new medical periodical. This effort represents a difficult challenge, but it will be an indispensable contribution that our Association will offer to physicians, specialists, and medical students.

Its purpose is to be an open stage for the reflection of the best materials from all areas of Internal Medicine, but especially those where multi-organ effects are intertwined or placed on top, since Internal Medicine is a very broad and challenging field. However, the evolution of time, technology, and the imperative for heightened professionalism across various domains have led to the emergence of distinct specialties, diverging from the Internal Medicine origin, thereby causing fragmentation within this field on a global scale. Therefore, it is necessary to renew this specialty, widely recognizing and accepting its universally acknowledged role in Medicine.

Even in our country this world practice was embraced by the eminent people of Internal Medicine such as Prof. Fejzi Hoxha and Dr. Sc. Hysni Rusi, dividing Internal Medicine into separate Internal Medicine Services, to then sub-specialization within these Services.

But the globalization of society, the change in lifestyle brought to the attention of policymakers and experts in the field the necessity of renewing the specialty of Internal Medicine, widely recognizing and accepting its main role in medicine. As a reflection of contemporary requirements, the re-creation of the Internal Medicine Service at University Hospital Center "Mother Teresa" of Tirana in 2004, under the leadership of Prof. Mihal Tase marked an important moment. Prof. Tase not only consolidated, but also elevated the Internal Medicine service to standards comparable to the equivalent Services in the world. The increase in the weight of Internal Medicine, as has been emphasized by the Ministry of Health in the National Health Strategy 2021-2030, presents a special challenge for young doctors to choose this difficult but also beautiful specialty.

The publication of this magazine symbolizes an important step in this direction. The Albanian Journal of Internal Medicine aims to serve as a scientific leader and will cover a wide range of medical fields, giving authors the opportunity to contribute value. The Scientific Editorial Board promises to maintain scientific standards, ensuring that published articles will maintain a high scientific rigor and practical relevance to current medicine.

The journal will focus on clinical studies, epidemiology, new treatments, preventive methods and any topic related to the Internal Medicine field. It aims to serve as an important source of scientific information for medical students, helping them to engage in scientific research and clinical studies. By offering articles from many medical disciplines, the Journal aims to cultivate interdisciplinary collaboration, a cornerstone for fostering innovative approaches in health studies and practice.

The Albanian Journal of Internal Medicine will be actively supported by a team of editors from various medical sub-fields, to bring contemporary and relevant content to all areas of Internal Medicine. All manuscripts submitted will be evaluated by the Scientific and Editorial Board, that includes national and international luminaries in the field.

I express my sincere gratitude to all esteemed professors and respected doctors, whether local or foreign, who have joined this great challenge of their own free will, which I am confident that we will win together.

We look forward to cooperating with each of you in realizing our common objective of turning this Journal into a forum for scientific discussion and dissemination of the latest scientific achievements.

Prof. Margarita Gjata Resuli
President of the Albanian Society of Internal Medicine

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FJALA PËRSHËNDETËSE

Të nderuar kolegë, partnerë, miq dhe lexues të ardhshëm të Revistës Shqiptare të Mjekësisë Interne,

Në emër të të gjithë kontribuesve të kësaj Reviste të re, dëshiroj të shpreh se jemi të vetëdijshëm mbi përgjegjësinë e rëndësishme që po ndërmarrim me krijimin e këtij publikimi mjekësor të ri. Kjo përpjekje paraqet një sfidë të vështirë, por do të jetë një kontribut i pamohueshëm që Shoqata jonë do t'iu ofrojë mjekëve, specialistëve dhe studentëve të Mjekësisë.

Qëllimi kryesor i kësaj reviste është të shërbejë si një platformë për shpërndarjen e hulumtimeve më të fundit në të gjitha fushat e Mjekësisë Interne, njohur si themeli i specialiteteve mjekësore që trajtojnë sëmundjet e brendshme. Megjithatë, evolucioni i kohës, teknologjia dhe nevoja për profesionalizëm të lartë në disa fusha kanë evoluar drejt krijimit të sub-specialiteteve të ndryshme, duke i larguar nga origjina e Mjekësisë Interne dhe duke shkaktuar kështu fragmentime brenda kësaj fushe në një shkallë globale. Edhe në vendin tonë, kjo praktikë Botërore u përqafua nga eminencat e Mjekësisë Interne të kohës si Prof. Fejzi Hoxha dhe Dr. Shk. Hysni Rusi, duke ndarë Mjekësinë Interne në Shërbime të veçanta të Sëmundjeve të Brendshme, për të kaluar më pas dhe në sub-specializime sipas këtyre Shërbimeve.

Por, globalizimi i shoqërisë, ndryshimi i stilit të jetesës risolli në vëmendjen e politikbërësve dhe ekspertëve të fushës domosdoshmërinë e rinovimit të specialitetit të Mjekësisë Interne, duke njohur dhe pranuar gjerësisht rolin e tij kryesor në mjekësi.

Si reflektim ndaj kërkesave bashkëkohore, rikrijimi i Shërbimit të Mjekësisë Interne në Qendrë Spitalore Universitare "Nënë Tereza" në vitin 2004, nën udhëheqjen e Prof. Mihal Tase, shënon një moment të rëndësishëm. Prof. Tase jo vetëm e konsolidoi, por edhe e ngriti shërbimin e Mjekësisë Interne në standarde të krahasueshme me Shërbimet homologe në botë.

Rritja e peshës së Mjekësisë Interne, siç është theksuar dhe nga Ministria e Shëndetësisë në Strategjinë Kombëtare të Shëndetësisë 2021-2030, paraqet një sfidë të veçantë për mjekët e rinj që të zgjedhin këtë specialitet të vështirë por edhe të bukur.

Fillimi i kësaj reviste simbolizon një hap të rëndësishëm në këtë drejtim. Revista Shqiptare e Mjekësisë Interne synon të shërbejë si një lider shkencor dhe do të përfshijë një gamë të gjerë fushash mjekësore, duke i dhënë mundësinë autorëve për të kontribuar me vlera. Bordi Editorial Shkencor premton të mbajë standarde shkencore, duke siguruar që artikujt e botuar të ruajnë një rigorozitet shkencor të lartë dhe domethënie praktike për aktualitetin mjekësor.

Revista do të përqendrohet në studime klinike, epidemiologji, trajtime të reja, metodat parandaluese dhe çdo temë të lidhur me problemet e Sëmundjeve të Brendshme. Ajo synon të shërbejë si një burim i rëndësishëm informacioni shkencor për studentët e mjekësisë, duke i ndihmuar ata të përfshihen në hulumtime shkencore dhe studime klinike. Duke ofruar artikuj nga shumë disiplina mjekësore, revista synon të kultivojë bashkëpunimin interdisiplinar, një gur themeli për nxitjen e qasjeve inovative në studimet dhe praktikën shëndetësore.
Revista Shqiptare e Mjekësisë Interne do të mbështetet aktivisht nga një ekip specialistësh të sub-specialiteteve të ndryshme mjekësore, për të sjellë përmbajtje bashkëkohore dhe me rëndësi për të gjitha fushat e Mjekësisë Interne. Të gjitha punimet e mbërritura do të vlerësohen nga Bordi Editorial dhe ai Shkencor që përfshijnë profesorë vendas dhe të huaj.

Unë shpreh falenderimin tim të sinqertë për të gjithë profesorët dhe mjekët e nderuar, brenda dhe jashtë vendit, që kanë pranuar me vullnetin e tyre këtë sfidë sa të vështirë por edhe të bukur.

Ne presim me padurim bashkëpunimin me secilin prej jush në realizimin e objektivit tonë të përbashkët për shndërrimin e kësaj Reviste në një forum të diskutimit shkencor dhe shpërndarëse të arritjeve shkencore më të fundit.

Prof. Margarita Gjata Resuli
Presidente e Shoqatës Shqiptare të Mjekësisë Interne

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1. Giuliano RP et al. N Engl J Med 2013; 369(22):2093–2104; and supplementary appendix. 2. Kato ET et al. J Am Heart Assoc 2016; 5(5). pii: e003432. 3. Ruff CT et al. Lancet 2015; 385(9984):2288–95.
4. Roteas®. Summary of Product Characteristics. 12/2021. 5. Steffel J et al. Eur Heart J 2018; 39:1330–1393.

TABLE OF CONTENTS

TO DO OR NOT TO DO A PHD?

Adela Perolla, Gentjan Asllanaj, Margarita Gjata Resuli
University of Medicine, Faculty of Medicine, Tirana Albania

Correspondent E-mail: adelaperolla19@gmail.com

Abstract
Deciding to embark on a Doctor of Philosophy journey is a significant life choice that necessitates a detailed evaluation of its influence on an individual's career path and personal development. This study delves into the intricacies of making such a critical decision, contrasting the internal and external motivations with the array of challenges and opportunities that come with doctoral studies. Through a comprehensive review of related literature, this research unpacks the dichotomy of the Doctor of Philosophy experience—its potential for deep academic engagement and personal transformation versus the obstacles of financial hardship, mental health concerns, and the uncertain job landscape for graduates. It also explores the effect of discipline-specific prospects, geographical disparities, and personal career goals on decision-making. The discussion broadens to examine how the alignment of doctoral efforts with long-term professional aims and the influence of academic mentorship shapes this crucial decision. Furthermore, it contemplates the changing dynamics of Doctor of Philosophy qualifications in the modern academic and professional context, advocating for a decision-making process that weighs both the intellectual satisfaction derived from research and the practical considerations after earning the degree. This literature review aims to illuminate the multifaceted factors that prospective doctoral candidates consider, assisting them in making well-informed decisions that align with their educational aspirations and life objectives.

Keywords: Doctor of Philosophy, decision-making, career development, challenges, opportunities, academic engagement, job market, mentorship.

TË BËSH APO TË MOS BËSH DOKTORATURË (PHD)?

Abstrakt
Vendimi për të nisur një udhëtim Doktorature është një zgjedhje jetësore e rëndësishme që kërkon një vlerësim të hollësishëm të ndikimit të tij në rrugëtimin profesional dhe zhvillimin personal të një individit. Ky studim zhytet në detajet e ndërmarrjes së një vendimi kaq kritik, duke krahasuar motivimet e brendshme dhe të jashtme me një sërë sfidash dhe mundësish që vijnë sëbashku me studimet doktorale. Përmes një rishikimi gjithëpërfshirës të literaturës së lidhur me këtë subjekt, ky hulumtim shpalos dikotominë e përvojës së Doktoraturës—potencialin për një angazhim të thellë akademik dhe për një transformim personal përballë pengesave të vështirësive financiare, çështjeve të shëndetit mendor dhe peizazhit të pasigurt të tregut të punës për të diplomuarit. Ai gjithashtu eksploron efektin e perspektivave specifike të disiplinës, ndryshimeve gjeografike dhe qëllimeve personale të karrierës në procesin e vendimmarrjes. Diskutimi zgjerohet për të ekzaminuar se si përshtatja e përpjekjeve doktorale me qëllimet afatgjata profesionale dhe ndikimi i mentorimit akademik e formësojnë këtë vendim jetësor. Për më tepër, ai reflekton mbi dinamikat në ndryshim , të kualifikimeve të Doktoraturës në

kontekstin modern akademik dhe profesional, duke avokuar për një proces vendimmarrjeje që merr parasysh kënaqësinë intelektuale që rrjedh nga kërkimi dhe konsideratat praktike pas marrjes së diplomës. Ky rishikim i literaturës synon të ndriçojë faktorët shumëdimensionalë që kandidatët potencialë për doktoraturë i marrin në konsideratë, duke i ndihmuar ata të bëjnë vendime të mirëinformuara dhe që përputhen me aspiratat e tyre arsimore dhe objektivat e jetës.

Fjalë kyçe: Doktoraturë, vendimmarrje, zhvillim karriere, sfida, mundësi, angazhim akademik, tregu i punës, mentorim.

Introduction

Deliberating on whether to undertake a Doctor of Philosophy (PhD) program is a decision of profound importance, involving substantial investment in time, finances, and personal effort. The pursuit of a PhD extends beyond academic achievement, significantly influencing one's career path and personal growth. It is imperative for individuals contemplating this significant academic journey to fully appreciate its implications, including the opportunities for career development, the potential to contribute significantly to one's field of study, and the challenges that may arise, such as impacts on mental well-being and financial considerations (1-3). As such, those considering a PhD must carefully evaluate these aspects, aligning them with their professional aspirations and readiness to meet the demanding requirements of doctoral research. This article is dedicated to an in-depth exploration and synthesis of varied viewpoints and rigorous research findings related to the dual aspects of pursuing a Doctor of Philosophy (PhD). Its primary aim is to dissect the intricate balance between the considerable benefits that accompany the completion of a doctoral program, such as enhanced professional trajectories, significant contributions to the body of knowledge, and the personal satisfaction derived from scholarly achievement, and the substantial challenges that candidates may encounter. These challenges range from the financial investment required to sustain several years of study, to the mental and emotional toll that the intensity of doctoral research can exact, alongside navigating the increasingly competitive landscape of academic and research-oriented employment markets. By weaving together evidence-based insights on these topics, the article seeks to present a nuanced and multifaceted perspective to individuals contemplating embarking on the rigorous journey toward a PhD. The ultimate goal is to provide these prospective doctoral candidates with a comprehensive understanding of the complexity of doctoral studies, thereby supporting them in making informed and strategic decisions that align with their long-term academic ambitions and professional aspirations, while also considering their personal well-being and financial planning.

The Value of a PhD

1. Career Advancements

Earning a Doctor of Philosophy (PhD) degree stands as a pivotal gateway to engaging in scholarly and investigative careers, often unlocking access to positions that typically necessitate such advanced qualifications. This prestigious academic credential symbolizes a comprehensive understanding of a particular field of study alongside the proficiency to perform autonomous, in-depth research. As such, it distinguishes individuals in the competitive landscapes of academia and specialized research sectors, where a PhD is frequently a fundamental requirement (4,5).

Within the academic sphere, possession of a PhD is almost universally required for tenure-track roles, including professorships and lectureships. These positions demand a robust commitment to advancing a discipline's body of knowledge through both teaching and the publication of novel research, as well as the mentoring of emerging scholars (6). The emphasis on a doctoral degree for these roles highlights the premium placed on the rigorous expertise and research competencies cultivated during the PhD journey, enabling individuals to contribute significantly to their academic fields.

Moreover, in research institutions and analytical think tanks, the PhD credential is esteemed for indicating an individual's capability for conducting detailed, pioneering studies that can lead to significant breakthroughs or enhancements within their specialization. Such roles often require a demonstrated history of research and scholarly publication—skills that are refined through the doctoral research process. Holders of a PhD are also in demand for their specialized knowledge, which is critical for leading major research initiatives, securing project funding, and engaging in collaborative projects at the international level (7, 8).

Beyond academia and research-focused entities, the PhD qualification is increasingly recognized in the industry, governmental, and non-profit sectors where advanced analytical skills and domain-specific knowledge are imperative. In these contexts, PhD-trained professionals contribute by spearheading innovation, shaping policy formulation, and addressing multifaceted challenges through research-driven methods (9).

Thus, pursuing a PhD does not merely open avenues into academic and research-centric positions but also furnishes individuals with the expertise and capabilities essential for excelling in these roles. It enables significant contributions to the advancement of knowledge and societal progress (2, 4,9).

2. Contribution to Knowledge

Doctoral students hold a pivotal role in the scholarly ecosystem, with the responsibility and privilege to not only assimilate existing knowledge but to extend the frontiers of understanding in their specialized fields. The doctoral journey, underscored by rigorous methodological training and scholarly inquiry, prepares these students to undertake research that can question and sometimes overturn long-held paradigms (10).

Through the PhD dissertation, an embodiment of years of dedicated research, doctoral candidates generate novel insights that often lead to the publication of findings in high-impact academic journals. These contributions are critical in paving new avenues for scholarly inquiry, thus serving as a springboard for subsequent intellectual endeavors within the discipline (11). Moreover, their investigative pursuits frequently result in methodological advancements, enriching the toolkit available for future research explorations (12).

The original research conducted by doctoral candidates does not exist in a vacuum but contributes to a dynamic knowledge base. By engaging with the academic community through presentations at conferences and collaborative projects, PhD students ensure that their research

findings percolate through and invigorate the scholarly dialogue, thereby fostering an environment conducive to innovation (13,14).

Furthermore, the scholarly output of doctoral research often transcends academic boundaries, impacting policy, industry standards, and societal norms. It is through this dissemination of knowledge that doctoral students contribute to the broader application of research, affecting change and informing decision-making processes in various sectors (15).

In light of these contributions, the pursuit of a doctoral degree is not only an individual scholarly endeavor but a commitment to the collective advancement of academia and society. It is a testament to the doctoral process's transformative power, both for the individual scholar and the wider intellectual community.

3. Personal Growth and Skills Development

A PhD education is quintessentially about nurturing a suite of advanced intellectual skills. Central among these is the development of robust critical thinking skills, which is indispensable for academic success and beyond. Doctoral candidates are systematically trained to evaluate and synthesize complex information, critique arguments rigorously, and construct well-founded positions on a variety of topics, and practices that are fundamental in scholarly research (16).

Additionally, the research skills fostered throughout the PhD process are comprehensive and versatile, ranging from the formulation of pertinent research questions to the meticulous application of methodological tools and techniques. Doctoral students become proficient in designing robust studies, adept at utilizing a spectrum of methodological approaches, and skilled in data analytics—abilities that enable them to derive meaningful interpretations and insights from their research endeavors (17).

Furthermore, PhD training is an exercise in cultivating sophisticated problem-solving skills. Through the course of their studies, doctoral students encounter a variety of research-related challenges, necessitating innovative solutions. They learn to apply creative reasoning and strategic thinking to navigate and resolve complex problems, skills that are transferable to numerous professional contexts (18).

The cumulative effect of this skill development is the production of scholars who are not only experts in their chosen field but also possess a transferable set of competencies that are highly valued in a multitude of professional domains. The process of acquiring a PhD is thus as much about mastering a specific area of knowledge as it is about developing a rich toolkit of cognitive and analytical skills that are the hallmark of scholarly and professional excellence.

Table 1. Key points Individuals considering a PhD must engage in a reflective process

Aspect	Details
Career Advancements	Opens doors to academic and research positions, offering unique career paths in academia and research.
Contribution to Knowledge	Provides the opportunity to contribute original research and new insights to the field.
Personal Growth and Skills Development	Cultivates critical thinking, advanced research methodologies, and problem-solving capabilities.
Time and Financial Investment	Requires consideration of program duration and potential financial commitments.
Emotional and Mental Health Considerations	Involves navigating stress and pressure that may impact mental health.
Job Market Saturation	Necessitates analysis of job market conditions and potential for overqualification in certain sectors.
Field of Study	Emphasizes the importance of aligning PhD focus with career prospects and personal interests.
Geographical Location	Highlights how the value of a PhD can differ based on regional academic and industry demands.
Personal Motivations and Goals	Encourages reflection on personal motivations and compatibility with career aspirations.

Making the decision

When contemplating a Doctor of Philosophy (PhD) program, individuals need to conduct a deliberate analysis of the potential advantages and the associated challenges, ensuring that such a pursuit aligns with their personal situation and long-term objectives. Prospective students must consider the professional enrichment offered by a PhD, including the opportunity for extensive research, the potential for academic tenure, and access to a network of scholarly peers (19). They must also assess the high levels of autonomy and the intellectual rigor required for producing original research, which can lead to significant personal and academic satisfaction (20).

Conversely, potential drawbacks, such as the time required to complete the degree, often spanning multiple years, the financial implications of foregoing full-time employment, and the possibility of accruing student debt, must be weighed (21). The process also demands considerable personal sacrifice and can impose stress, which can affect one's mental health and well-being (22). As such, alignment with personal values and career goals is paramount.

Individual motivations for undertaking a PhD—whether for the pursuit of knowledge, a passion for research, or career progression—must be critically evaluated alongside the practical realities of post-PhD employability and the current state of the job market within one's field (9). It is crucial to reflect on the potential impact on one's personal life and consider support systems available during and after the PhD process.

In essence, the decision to pursue a PhD should be informed by a strategic consideration of how it complements one's academic aspirations, professional trajectory, and personal life. This contemplative approach to decision-making, informed by a thorough understanding of the PhD journey's demands and benefits, is imperative for ensuring that the commitment to doctoral study is in harmony with one's broader life plans (2).

Conclusion

In summary, the choice to pursue a doctoral degree is a critical one, with substantial implications for professional development and personal fulfillment. The PhD journey presents opportunities for specialized skill development and can pave the way to academic and research positions, balanced by significant demands on time, finances, and personal well-being.

Individuals considering a PhD must engage in a reflective process, carefully examining how the degree aligns with their unique professional objectives and personal circumstances. It is essential to seek guidance from experienced academics within their discipline, whose insights can shed light on the doctoral experience and the post-graduation landscape.

In essence, thorough reflecti on and mentorship are invaluable as prospective candidates approach this decision, enabling them to chart a course that is professionally rewarding and personally enriching.

References

1. Lovitts, B. E. (2001). Leaving the Ivory Tower: The Causes and Consequences of Departure from Doctoral Study. Lanham: Rowman & Littlefield.
2. Golde, C. M. (2005). The Role of the Department and Discipline in Doctoral Student Attrition: Lessons from Four Departments. The Journal of Higher Education, 76, 669-700. http://dx.doi.org/10.1353/jhe.2005.0039
3. Evans, T., Bira, L., Gastelum, J. *et al.* Evidence for a mental health crisis in graduate education. *Nat Biotechnol* **36**, 282–284 (2018). https://doi.org/10.1038/nbt.4089
4. Cyranoski, D., Gilbert, N., Ledford, H., Nayar, A., & Yahia, M. (2011). Education: The PhD factory. *Nature*, *472*(7343), 276–279. https://doi.org/10.1038/472276a
5. Matthew M. Mars & Sheila Slaughter & Gary Rhoades, 2008. "The State-Sponsored Student Entrepreneur," The Journal of Higher Education, Taylor & Francis Journals, vol. 79(6), pages 638-670, November.
6. Gould J. (2015). How to build a better PhD. *Nature*, *528*(7580), 22–25. https://doi.org/10.1038/528022a
7. Horta, H. (2009). Global and National Prominent Universities: Internationalization, Competitiveness and the Role of the State. *Higher Education*, *58*(3), 387–405. http://www.jstor.org/stable/40269190
8. Nerad, M. (2010). Globalization and the Internationalization of Graduate Education: A Macro and Micro View. Canadian Journal of Higher Education, 40(1), 1–12. https://doi.org/10.47678/cjhe.v40i1.1566

9. Sauermann H, Roach M (2012) Science PhD Career Preferences: Levels, Changes, and Advisor Encouragement. PLoS ONE 7(5): e36307. https://doi.org/10.1371/journal.pone.0036307
10. James, R., & Baldwin, G. (1999). Eleven Practices of Effective Postgraduate Research Supervisors. Melbourne: The Centre for the Study of Higher Education & The School of Graduate Studies, University of Melbourne. http://melbournecshe.unimelb.edu.au/__data/assets/pdf_file/0004/1761502/11practices.pdf
11. Thomson, P., & Walker, M. (2010). Doctoral education in context: The changing nature of the doctorate and doctoral students. In M. Walker, & P. Thomson (Eds.), The Routledge doctoral supervisor's companion (pp. 9-26). Abingdon: Routledge.
12. Peters, M. A., & Roberts, P. (2008). "Preliminary Material". In Neoliberalism, Higher Education and Research. Leiden, The Netherlands: Brill. https://doi.org/10.1163/9789087906306_001
13. Herrington, J., McKenney, S., Reeves, T. C., & Oliver, R. (2007). Design-based research and doctoral students: Guidelines for preparing a dissertation proposal. In C. Montgomerie, & J. Seale (Eds.), *Proceedings of World Conference on Educational Multimedia, Hypermedia and Telecommunications 2007* (pp. 4089-4097) http://ro.ecu.edu.au/ecuworks/1612/
14. Goff, W. M., & Getenet, S.. (2017). Design based research in doctoral studies: Adding a new dimension to doctoral research. International Journal of Doctoral Studies, 12, 107-121. Retrieved from http://www.informingscience.org/Publications/3761
15. Sampson, H. (2019). 'Fluid fields' and the dynamics of risk in social research. Qualitative Research, 19(2), 131-147. https://doi.org/10.1177/1468794117746085
16. Ennis, R. H. (1993). Critical thinking assessment. *Theory Into Practice*, *32*(3), 179–186. https://doi.org/10.1080/00405849309543594
17. Creswell. J.W. and Creswell, J.D. (2017) Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. 4th Edition, Sage, Newbury Park.
18. Polya, G. (1945). *How to solve it; a new aspect of mathematical method.* Princeton University Press.
19. Lovitts *, B. E. (2005). Being a good course-taker is not enough: a theoretical perspective on the transition to independent research. Studies in Higher Education, 30(2), 137–154. https://doi.org/10.1080/03075070500043093
20. Walker, George & Golde, Chris & Jones, Laura & Bueschel, Andrea & Hutchings, Pat. (2009). The Formation of Scholars: Rethinking Doctoral Education for the Twenty-First Century. International Journal for Academic Development. 14.
21. Nettles, M. T., & Millett, C. M. (2006). Three magic letters: Getting to Ph.D. Baltimore, MD: The Johns Hopkins University Press.
22. Stubb, J., Pyhältö, K., & Lonka, K. (2011). Balancing between inspiration and exhaustion: PhD students' experienced socio-psychological well-being. *Studies in Continuing Education*, *33*(1), 33–50. https://doi.org/10.1080/0158037X.2010.515572

THE IMPORTANCE OF EVALUATING MICROALBUMINURIA IN HYPERTENSIVE PATIENTS: A SYSTEMATIC REVIEW

Irida Kecaj, Ergita Nelaj, Ilir Gjermeni, Pandush Pojani, Margarita Gjata Resuli
Service of Internal Medicine and Hypertension, University Hospital Center "Mother Teresa", Tirana, Albania

Correspondent E-mail: irida.kecaj@yahoo.com.

Abstract

Microalbuminuria is a marker for generalized vascular endothelial dysfunction, that is considered an independent predictor of increased risk for cardiovascular morbidity and mortality in patients with hypertension. Numerous clinical studies in non-diabetic populations have shown an association between microalbuminuria and cardiovascular risk factors, target organ damage, and the presence of cardiovascular disease. Microalbuminuria occurs in approximately 11% to 40% of patients with essential hypertension. Treatment with an angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has shown superiority over other antihypertensive drugs in reducing urine albumin excretion and may prove to be a more targeted approach to reducing cardiovascular risk. Microalbuminuria can be considered not only a risk factor for progressive renal damage, but also a provider of an integrated assessment of long-term damage to the cardiovascular system. That is why it is used in cardiovascular risk assessment clinics. Whether targeted treatment of microalbuminuria in the non-diabetic population reduces cardiovascular morbidity and mortality, remains to be proven. However, there is a general consensus recommending the identification and quantification of microalbuminuria as an important, cost-effective examination that helps evaluate overall cardiovascular risk and identify high-risk patients for whom additional preventive and therapeutic measures are advisable.
Keywords: microalbuminuria, albumin creatinine ratio, hypertension, cardiovascular risk.

RËNDËSIA E VLERËSIMIT TË MIKROALBUMINURISË NË PACIENTËT HIPERTENSIVË: RISHIKIM LITERATURE

Abstrakt

Mikroalbuminuria është një vlerësues i disfunksionit endotelial vaskular, që konsiderohet si një parashikues i pavarur i rrezikut të rritur për mortalitet dhe morbiditet kardiovaskular në pacientët me hipertension. Një numër i madh studimesh klinike në popullsinë jo-diabetike kanë treguar një lidhje midis mikroalbuminurisë dhe faktorëve të rrezikut kardiovaskular, dëmtimit të organeve target dhe pranisë së sëmundjeve kardiovaskulare. Mikroalbuminuria ndodh në rreth 11% deri në 40% të pacientëve me hipertension primar. Trajtimi me frenues të enzimës konvertuese të angiotenzinës (shkurtimi në Anglisht ACE-I) dhe një bllokues të receptorit të angiotenzinës (shkurtimi në Anglisht ARB) ka treguar epërsi mbi barna të tjerë antihypertensive, në reduktimin e ekskretimit të albuminës në urinë dhe mund të provohet të jetë një qasje më objektive për zvogëlimin e rrezikut kardiovaskular. Mikroalbuminuria mund të konsiderohet, jo vetëm si një faktor rreziku për dëmtimin progresiv renal, por edhe si një mundësues i një vlerësimi

gjithëpërfshirës të dëmtimit afatgjatë të sistemit kardiovaskular. Për këtë është përdorur në klinikat e vlerësimit të rrezikut kardiovaskular. Mbetet për t'u provuar, nëse trajtimi objektiv i mikroalbuminurisë në popullsinë jodiabetike zvogëlon morbiditetin dhe mortalitetin kardiovaskular. Megjithatë, ka një konsensus të përgjithshëm që rekomandon njohjen dhe vlerësimin e mikroalbuminurisë, si një ekzaminim të rëndësishëm dhe kosto-efektiv, që ndihmon në vlerësimin e përgjithshëm të rrezikut kardiovaskular dhe njohjen e pacientëve me rrezik të lartë, për të cilët janë të këshillueshme masat shtesë parandaluese dhe terapeutike.

Fjalë kyçe: Mikroalbuminuria, Raporti albuminë/kreatininë, Hipertensioni, Risku kardiovaskular.

Introduction

Microalbuminuria (MAU) is defined as an amount of urinary albumin excretion (UAE) between 30 to 300 mg in an overnight collection or a urinary albumin/creatinine ratio (UACR) of 30-300 mg/g (3.5–30 mg/mmol in women, 2.5–30 mg/mmol in men), in the absence of urinary tract infection and acute illness, including myocardial infarction. MAU is an established marker of early renal disease and usually develops in terms of glomerular basement membrane dysfunction (GBM), allowing albumin entrance into the urine (1, 2). Normal urinary albumin excretion varies between 1 and 22 mg/day and can be influenced by changes in posture, exercise, and blood pressure (2). MAU does not present with any specific symptoms and mainly occurs in the absence of any serious underlying renal disease. The most common causes include essential hypertension, glucose intolerance, type 1 or type 2 diabetes, and metabolic syndrome. Epidemiological studies of MAU reveal a close association between systemic endothelial dysfunction and vascular disease. Numerous studies have demonstrated that MAU serves as a powerful predictor of cardiovascular disease onset, progression and mortality in adults (3-5). Post-hoc analyses of major clinical trials indicate that UAE levels, even below the cut-off values used to define MAU, correlate with an increased rate of cardiovascular disease, irrespective of the presence of existing kidney disease or diabetes (6-9). However, the exact pathophysiology of this relationship is under investigation. These findings suggest that detecting MAU may be the most reliable indicator of an increased global cardiovascular risk in a given patient. Although reducing arterial pressure remains the gold standard for cardiovascular and renal protection (10), controlling it within strict values does not completely eliminate albuminuria and MAU in patients with hypertension, thus giving special importance to therapeutic strategies for the optimal reduction of microalbuminuria. The LIFE study demonstrated that reducing urinary protein excretion in both diabetic and non-diabetic patients during treatment translates to a reduction in cardiovascular events and a slower progression of renal disease (11). Screening for MAU is recommended by several expert committees and associations, providing clinicians with prognostic information concerning cardiovascular risk and assisting in guiding therapy. The European Society of Cardiology (ESC) guidelines recommend assessing the UACR in all hypertensive patients (12).

The aim of this article is to provide updated and comprehensive information about the relationship between MAU, hypertension, and cardiovascular disease, as well as the importance of evaluating MAU in hypertensive patients.

Microalbuminuria and hypertension

The prevalence of MAU ranges from 11% to 40% in patients with essential hypertension (13) and increases with age and severity of hypertension. The finding that MAU in hypertensive patients is an independent risk factor for cardiovascular disease, suggests a relationship between vascular leakage in the glomeruli and vascular damage. A significant increase in intracapillary pressure or structural damage of the glomerular membrane may lead to the leakage of protein from the plasma into Bowman's space, resulting in the development of microalbuminuria, which may vary with the severity of hypertension. Changes in hemodynamics that occur in hypertension (elevation in intraglomerular pressure and generalized angiopathy due to endothelial dysfunction that causes renal and systemic transvascular albumin leakage), are the most probable causes of MAU in hypertensive patients (14).

The presence of MAU in patients with essential hypertension serves as a marker of early intrarenal vascular dysfunction (7). A study published by Catena et al. revealed that elevated UACR was associated with significant and progressively higher blood pressure (BP), HDL-cholesterol, and plasma aldosterone levels, and with lower glomerular filtration. MAU was detected in 17% of 242 hypertensive patients, who had significantly higher BP and plasma aldosterone levels (178 ± 113 vs. 128 ± 84 pg/ml; P = 0.001), and lower glomerular filtration compared with patients without microalbuminuria. UACR was directly and independently correlated with BP and plasma aldosterone levels. In conclusion, the presence of low-grade albuminuria independently correlates with increased plasma aldosterone, suggesting a contribution of aldosterone to the early glomerular changes seen in hypertensive nephropathy (15). Numerous studies have provided evidence that hypertensive target organ damage is more common in microalbuminuric patients. MAU correlates with early signs of extra-renal organ damage, including left ventricular hypertrophy and dysfunction, carotid artery thickening and plaque formation, and a higher incidence of hypertensive retinopathy (16). A recent analysis of the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study was the first to address the issue of the prognostic value of UAE in a very large cohort (n= 8206) entirely composed by hypertensive subjects, demonstrating that both the frequency and severity of MAU were linked to greater LV mass and dysfunction. This correlation was independent of systolic BP, age, race, or coexisting diabetes (8). MAU has been identified as a predictor for silent myocardial ischemia. In a large nondiabetic population, patients with microalbuminuria and ST-T changes on their electrocardiograms had markedly increased risks for cardiovascular and all-cause mortality compared to patients with the same electrocardiographic changes but no microalbuminuria (17). Due to the significant association between microalbuminuria and carotid artery intima-media thickness observed in patients with hypertension, MAU may be a marker for early development of carotid artery atherosclerosis (16). The latest ESC hypertension guidelines advocate for the inclusion of hypertension-mediated organ damage (HMOD) assessment, notably focusing on the presence of MAU, left ventricular hypertrophy and arterial stiffness, in order to enhance the accuracy of cardiovascular risk evaluation during blood pressure management. Early screening of hypertensives for MAU and prompt treatment of positive cases might reduce the disease burden related to severe chronic kidney disease and cardiovascular events in the community. Given the substantial evidence highlighting the importance of MAU and hypertension in cardiovascular disease, both the American College of Cardiology/American Heart Association and the International Society of Hypertension recommend routine urine dipstick testing or UACR testing to assess MAU (12,18).

Effect of various antihypertensive drugs on microalbuminuria.

Although numerous studies have demonstrated the impact of MAU on cardiovascular risk, it remains unclear whether the reduction of MAU leads to a corresponding reduction in this risk. Multiple clinical trials have shown the efficacy of several antihypertensive drugs in reducing MAU. Among available antihypertensive drugs, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) seem to be superior to other antihypertensive drugs in reducing UAE (19-23). In a large study conducted in African American subjects (AASK study) with primary hypertension, ramipril was more effective than amlodipine in reducing UAE (20). Furthermore, the LIFE trial revealed that subjects with the lowest CV event rates exhibited the most significant reduction in UAE when treated with losartan-based regimen, compared to baseline. Treatment with losartan resulted in a greater reduction in albuminuria compared with beta-blocker therapy, despite equivalent decreases in blood pressure (24). The Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND IT) enrolled patients with baseline MAU and randomized them to the angiotensin-converting enzyme inhibitor fosinopril or a matching placebo. The study noted that the fosinopril-treated subjects had a 26% reduction in albumin excretion, which was less than that observed in the LIFE trial. However, this reduction did not correlate with a decrease in CV mortality or hospitalization (25). A study on the reduction of MAU among hypertensive patients using triple combination therapy (perindopril 4 mg, amlodipine 5 mg and indapamide 1.25 mg) (26) demonstrated a significant reduction in blood pressure with the use of triple combination therapy. Additionally, MAU reverted to normal albumin excretion in urine, which was statistically significant ($p < 0.01$). This was the most significant and convincing finding. Dihydropyridine calcium antagonists have failed to reduce proteinuria in patients with type 2 diabetes. On the other hand, non-dihydropyridine calcium channel blockers (CCBs) have been proven to have a therapeutic effect on MAU in type 2 diabetes (27).

Conclusion

By demonstrating a strong association between MAU and hypertension, evaluating the presence of MAU becomes a simple and accurate method to detect hypertensive patients at high risk for cardiovascular and potential renal damage. Early detection of microalbuminuria has been extensively studied and observed to aid in halting the progression of the underlying disease. An interprofessional team is crucial for early screening and management of microalbuminuria. Healthy lifestyle changes and effective antihypertensive management can be implemented through more aggressive BP controls. Additionally, MAU can indirectly assist in reducing CVD risk in patients, serving not only as a predictor for CVD, but also as a target for therapy.

Conflicts of Interest: No conflict of interest

References

1. Microalbuminuria. Rohan M. Prasad; Atul Bali; Richa Tikaria. Last Update: May 30, 2023.
2. Totto R. Microalbuminuria: Definition, Detection, and Clinical Significance. J Clin Hypertens (Greenwich). 2004; 6:2-7.

3. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073-81. doi: 10.1016/S0140-6736(10)60674-5.
4. Hillege HL, Fidler V, Diercks GF, Gilst WH, Zeeuw D, Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–1782. doi: 10.1161/01.CIR.0000031732.78052.81.
5. Volpe M. Microalbuminuria screening in patients with hypertension: recommendations for clinical practice. Int J Clin Pract. 2008;62:97-108.
6. Matsushita K, Velde M, Astor BC, Woodward M, Levey AS, Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5.
7. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–426. doi: 10.1001/jama.286.4.421.
8. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, Beevers G, Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med. 2003;139:901–906.
9. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation. 2004;110:32–35. doi: 10.1161/01.CIR.0000133312.96477.48.
10. Chobanian, G.L. Bakris, H.R. Black, et al.The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA, 289 (2003), pp. 2560-2572
11. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux R, de Faire U, Fyhrquist F, Julius S, Kjeldsen S, Lederballe-Pedersen O, Nieminen M, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension. 2005;45:198-202.
12. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International Society of Hypertension Global Hypertension practice guidelines.Hypertension. 2020; 75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026.
13. Rossa TT, Palatini P: Clinical value of microalbuminuria in hypertension. J Hypertens 2000;18:645–654.
14. Microalbuminuria and cardiovascular risk. Janaka Karalliedde, Giancarlo Viberti. American Journal of Hypertension, Volume 17, Issue 10, October 2004, Pages 986–993, https://doi.org/10.1016/j.amjhyper.2004.08.010.

15. Microalbuminuria and plasma aldosterone levels in nondiabetic treatment-naïve patients with hypertension. Cristiana Catena 1, GianLuca Colussi, Flavia Martinis, Marileda Novello, Leonardo A Sechi. 2017 Dec;35(12):2510-2516. doi: 10.1097/HJH.0000000000001476.
16. Evaluation of subclinical organ damage for risk assessment and treatment in the hypertensive patient: role of microalbuminuria. Roberto Pontremoli 1, Giovanna Leoncini, Francesca Viazzi, Elena Ratto, Valentina Vaccaro, Valeria Falqui, Angelica Parodi, Novella Conti, Cinzia Tomolillo, Giacomo Deferrari. 2006 Apr;17(4 Suppl 2):S112-4. doi: 10.1681/ASN.2005121327.
17. Diercks GF, van Boven AJ, Hillege HL, Janssen WM, Kors JA, de Jong PE, Grobbee DE, Crijns HJ, van Gilst WH: Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population: the PREVEND (Prevention of REnal and Vascular ENdstage Disease) study. Eur Heart J 2000;21:1922–1927.
18. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065.
19. Ruilope LM, Alcazar JM, Hernandez E, Praga M, LaheraV, Rodicio JL. Long-term influences of antihypertensivetherapy on microalbuminuria in essential hypertension.Kidney Int Suppl 1994; 45: S171–3.94.
20. Agodoa LY, Appel L, Bakris GL,et al. African AmericanStudy of Kidney Disease and Hypertension (AASK) StudyGroup. Effect of ramipril versus amlodipine on renaloutcomes in hypertensive nephrosclerosis. JAMA 2001;285: 2719–28.95.
21. Monster TB, Janssen WM, de Jong PE, de Jong-van denBerg LT PREVEND Study Group. The impact of anti-hypertensive drug group on urinary albumin excretion in a non-diabetic population. Br J Clin Pharm 2002; 53: 31–6.96.
22. Garg J, Bakris GL. Angiotensin converting enzyme inhibi-tors or angiotensin receptor blockers in nephropathy from type 2 diabetes. Curr Hypertens Rep 2002; 4: 185–90.97.
23. Pisoni R, Ruggenenti P, Remuzzi G. Renoprotectivetherapy in patients with non-diabetic nephropathies. Drugs2001; 61: 733–45.98.
24. Ibsen H, Wachtell K, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y; LIFE substudy. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens. 2004;22:1805-11.
25. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110:2809–2816.
26. Arun, Abhishek, Study on reduction of microalbuminuria amongst hypertensive patients with use of triple combination therapy (triplixam). Journal of Hypertension 39: pp e31, April 2021. | DOI: 10.1097/01.hjh.0000744680.94912.ce

27. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int. 1996;50:1641-50.

ULTRASOUND OF CAROTID ARTERIES, WHAT ARE PLAQUES, STENOSIS: LATEST NEWS AND FUTURE TASKS

Ilir Gjermeni[1], Eliona Gjermeni[2], Ledio Çollaku[1], Eneida Hoxha[1], Margarita Gjata Resuli[1]
[1]Service of Internal Medicine and Hypertension, University Hospital Center "Mother Teresa", Tirana, Albania
[2]Specialties Health Center No. 3, Tirana, Albania

Correspondent E-mail: ilirgjermeni@yahoo.it

Abstract
In recent decades, cardiovascular diseases are the main cause of mortality in developed and developing countries. The diagnosis and especially the assessment of the degree of risk of these pathologies constitute today the challenges that modern medicine dictates to us. One of the imaging examinations that is receiving attention in recent years in terms of cardiovascular risk assessment is the doppler ultrasound of carotid arteries. The knowledge about this examination, the indications and especially the correct interpretation of the data, will be a valuable tool in helping the work of the clinician.

Keywords: Doppler Ultrasound; Carotid arteries; Carotid plaque; Carotid stenosis.

EKOGRAFIA E ARTERIEVE KAROTIDE, ÇFARË JANË PLLAKAT, STENOZAT: TË REJAT E FUNDIT DHE DETYRAT E TË ARDHMES

Abstrakt
Në dekadat e fundit sëmundjet kardiovaskulare janë shkaku kryesor i vdekshmërisë në vendet e zhvilluara dhe në ato në zhvillim. Diagnostikimi dhe sidomos vlerësimi i shkallës së rrezikut të këtyre patologjive, përbëjnë sot sfidat që na dikton mjekësia bashkëkohore. Një nga ekzaminimet imazherike që po merr vëmendje vitet e fundit në drejtim të vlerësimit të rrezikut kardiovaskular është edhe ekografia doppler e arterieve karotide.
Sfondi: Ekografia Doppler është zhvilluar në sajë të bashkëpunimit shumëvjeçar midis mjekëve dhe inxhinierëve. Që prej futjes në praktikën klinike në vitet '70 të shekullit të kaluar, ky ekzaminim ka përjetuar përmirësime të ndjeshme në teknikë dhe është sot një nga testet më të besueshme dhe praktike në vlerësimin e sëmundjeve vaskulare. Duke ndërthurur imazhet *B-mode* dhe teknologjinë Doppler, ekografia Doppler e arterieve karotide lejon mjekun të vlerësojë nga ana sasiore dhe cilësore pllakat dhe stenozat e arterieve karotide. Qëllimi i këtij artikulli është të njohë mjekët klinicistë me indikacionet, interpretimin e të dhënave dhe të rejat e fundit për ekografinë Doppler të arterieve karotide.
Metodat. Rishikim i literaturës dhe imazhe ekografike nga puna me pacientë në Shërbimin e Mjekësisë Interne dhe Hipertonisë në Qendrën Spitalore Universitare "Nënë Tereza", Tiranë.
Përfundim. Ekziston nevoja e ndërtimit të një protokolli mjekësor kombëtar në lidhje me shkallëzimin e pllakave dhe stenozave të arterieve karotide, për të bërë të mundur më tej edhe një

vlerësim të standardizuar të riskut kardiovaskular të pacientit, bazuar edhe në vecoritë e popullatës shqiptare.

Fjalë kyçe: Ekografia Doppler; Arteriet karotide; Pllakat karotide; Stenozat karotide.

Introduction

Anatomy of the carotid artery

CCA

The common carotid arteries (CCA) are paired branchless arteries of the neck that supply blood to the head, face and neck. Each common carotid bifurcates into internal and external carotid arteries. Although the left and right common carotid arteries follow the same course through the neck, their origin differs. On the left, the CCA arises directly from the aortic arch whereas, on the right, the origin is from the brachiocephalic trunk. The left CCA can be thought of as having two distinct parts: thoracic and cervical. Since the right CCA arises cranially, it only really has a cervical portion. The cervical portion of both CCAs follows a similar course. Each vessel passes obliquely upwards from behind the sternoclavicular joint to the level of the upper border of the thyroid cartilage, at approximately the C4 level (Fig. 1) (1).

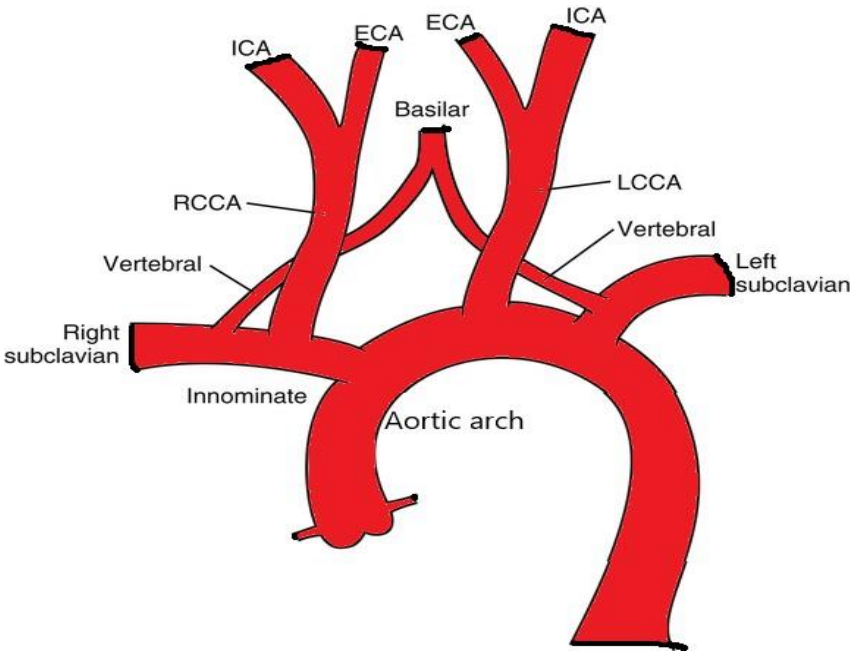


Figure 1. Carotid artery anatomy

The internal carotid artery (ICA) is one of two terminal branches of the common carotid artery (CCA) which supplies intracranial structures.

Origin

The common carotid artery branches to form the internal carotid artery (ICA) and the external carotid artery (ECA). Immediately after its origin, the ICA has an expansion called the carotid bulb or sinus. In the carotid body there is a small collection of chemoreceptor cells located immediately after the bifurcation (2).

In most cases, the carotid bifurcation occurs between the levels of the C3 and C5 vertebrae, or between the levels of the hyoid bone and the upper border of the thyroid cartilage. However, there is a wide variation (2).

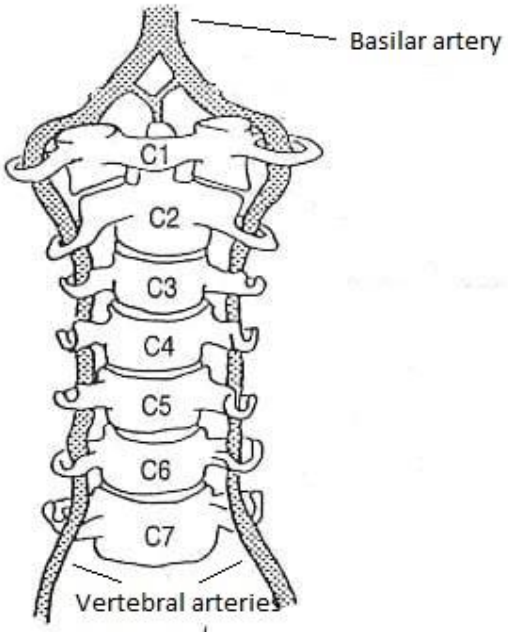


Figure 2. Vertebral arteries anatomy

Vertebral artery

Paired vertebral arteries provide blood supply for the upper part of the spinal cord, brainstem, cerebellum, and posterior part of the brain. Each artery originates from the first part of the subclavian artery, it then courses superiorly along the sides of the neck, merging with its companion at the pons level to form the single, midline basilar artery as shown in Fig. 2 (3).

Circle of Willis

The basilar artery and ICA give off numerous communicating branches which anastomose with each other at the base of the brain, forming the hexagonal vascular network called the circle of Willis. The circle of Willis connects the anterior and posterior circulations of the brain. This reflects the importance of the vertebral artery for the human body.

The circle of Willis (cerebral arterial circle or circulus arteriosus) is an anastomotic ring of arteries located at the base of the brain. This arterial anastomotic circle connects the two major arterial systems to the brain, the internal carotid arteries and the vertebrobasilar (vertebral and basilar arteries) systems. It is formed by four paired vessels and a single unpaired vessel with numerous branches that supply the brain (Fig. 3) (3).

The main function of the circle of Willis is to provide a collateral blood flow between the anterior and posterior arterial systems of the brain. Additionally, it offers the alternate blood flow pathways between the right and left cerebral hemispheres. This way the circle protects the brain from ischemia and stroke in cases of vascular obstruction or damage (3).

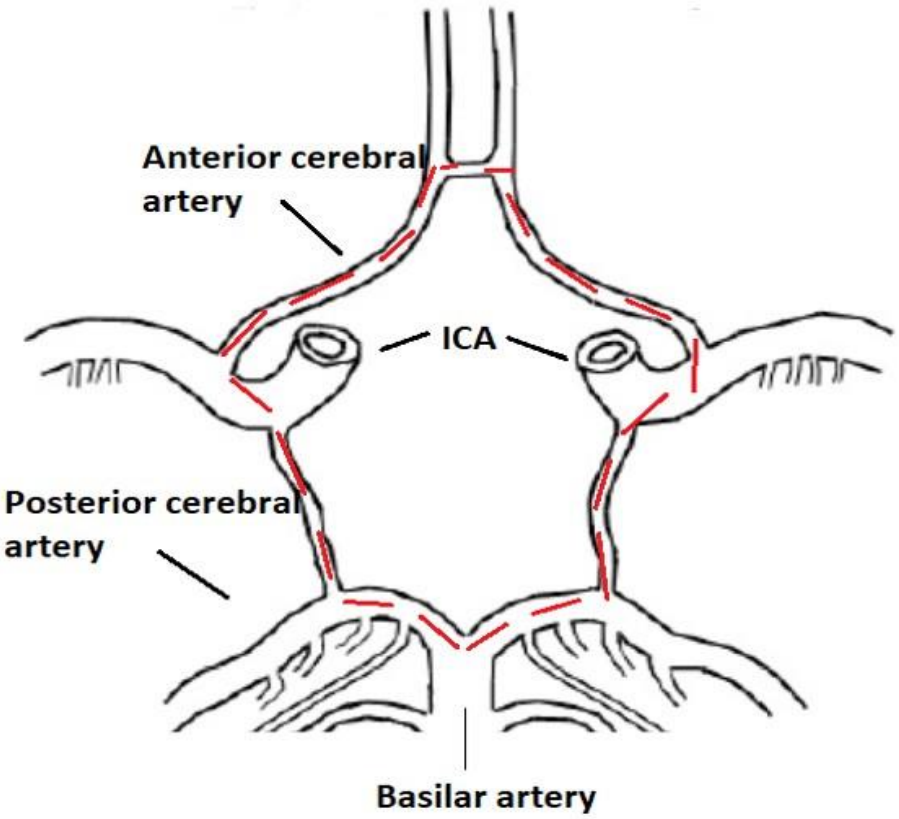


Figure 3. Circle of Willis

Carotid ultrasound

Carotid ultrasound, also called Doppler ultrasound or carotid duplex ultrasound, (DUS) is a painless and harmless test to evaluate the carotid arteries. Carotid ultrasound assesses the presence of atherosclerotic plaques in the arteries. The plaque consists of substances such as: cholesterol, calcium, different cells, and an increase in its size can cause narrowing of the lumen of the diseased artery (4).

Common Indications

Common indications for performing this examination include:

- Transient ischemic attacks (TIA)
- Amaurosis fugax
- Carotid bruit
- Cerebrovascular Accident (CVA)
- Follow-up of known carotid stenosis
- Post intervention follow-up e.g. carotid endarterectomy, stent or bypass

- Trauma in the distribution of the carotid artery e.g. suspected dissection, arteriovenous fistula or pseudoaneurysm
- Pre-operative assessment for high risk patients e.g. coronary artery bypass surgery (CABG)
- Pulsatile neck masses
- Evaluation of suspected subclavian steal syndrome
- Pre- maxillo-facial surgery (5)
- Dizziness alone is not sufficient indication for this exam (6).

Contraindications and Limits

Contraindications for extracranial cerebrovascular duplex ultrasound are few; however, some limitations exist and may include the following:

- Patients with short, thick muscular necks
- Patients who have had recent surgery, ultrasound visualisation may be limited due to oedema, haematoma, surgical staples, dressings etc
- Calcified plaque may cause acoustic shadowing limiting Doppler and B-mode image assessment
- Patients who are unable to lie flat due to pre-existing co-morbidities e.g. chronic obstructive pulmonary disease (COPD) and arthritis – although these patients may be able to tolerate being examined seated in a chair or with the head of the bed raised
- Patients who are unable to cooperate or those with involuntary movements
- Examinations undertaken portably at the patient's bedside may be limited due to equipment and room dimensions (5).

General Guidelines:

A complete examination includes evaluation of the bilateral common, extracranial internal carotid, and proximal external carotid arteries as well as the extracranial portions of bilateral vertebral arteries.

•The examination must be bilateral unless otherwise contraindicated

•A complete examination includes evaluation of the entire course of the accessible portions of each vessel

•Variations in technique must be documented (i.e., stents) (6).

Measurement of intima media thickness

Intima-media thickness (IMT) is a marker of subclinical atherosclerosis (asymptomatic organ damage) and should be evaluated in every asymptomatic adult or hypertensive patient at moderate risk for cardiovascular disease. Intima-media thickness values of more than 0.9 mm (ESC) or over the 75th percentile (ASE) should be considered abnormal. A carotid artery ultrasound scan is the method of choice, and results are reliable, provided certain standards are followed (7).

Atherosclerosis most often develops gradually and slowly, starting from childhood and proceeding into adulthood with varying velocity and susceptibility to complications. The first structural change that can be detected in atherosclerosis is an increase in IMT.

Intima-media thickness is an important atherosclerotic risk marker. However, this increase is not synonymous with subclinical atherosclerosis, but is related to it. Indeed, increase in IMT is also the result of nonatherosclerotic processes such as smooth muscle cell hyperplasia and fibrocellular hypertrophy leading to medial hypertrophy and compensatory arterial remodeling. Therefore this process may be an adaptive response to changes in flow, wall tension, or lumen diameter. The uniform thickening progresses in straight arterial segments as the patient ages and all known vascular risk factors accelerate this process. Therefore IMT is an important atherosclerotic risk marker but cannot be accepted as a risk factor and should not be subjected to treatment (7).

How is the measurement done?

IMT is defined as a double-line pattern visualised by echo 2D on both walls of the common carotid artery (CCA) in a longitudinal view as shown in Figure 4. Two parallel lines (leading edges of two anatomical boundaries) form it: lumen-intima and media-adventitia interfaces (7).

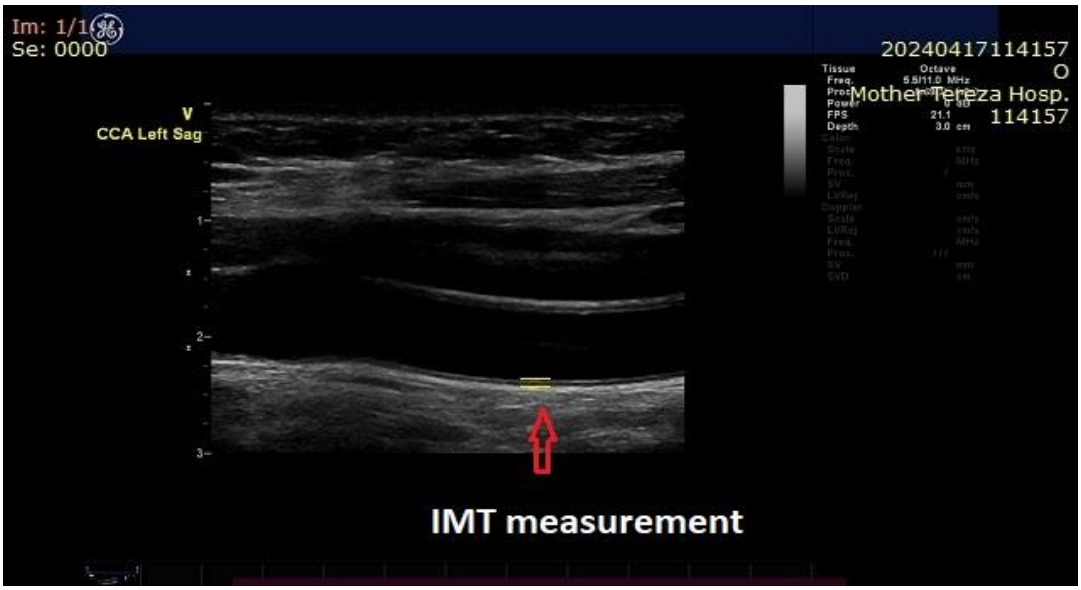


Figure 4. Intima-media thickness measurement

IMT is measured as the distance between lumen-intima (first yellow line) and media-adventitia (second yellow line) interfaces (7).

Where should the measurement be done?

The measurement is made at a distance of 10-20 mm from the branching of the CCA to the ICA and ECA. One of the main problems in interpreting IMT results from clinical trials is the differences in measurement methodology. These discrepancies can refer to either one or more of these parameters: the precise definition of the investigated carotid segment, the use of mean or maximal IMT, the measurement of near and far wall or only far wall IMT, the insonation at a single or different angles, employing manual tracking or an automated software, including

carotid plaques or not and uni- or bilateral measurements. To avoid this problem standards for IMT measurement have been developed (7). According to recent guidelines, an IMT >1.5 mm thick will be classified as plaque (Fig. 5).

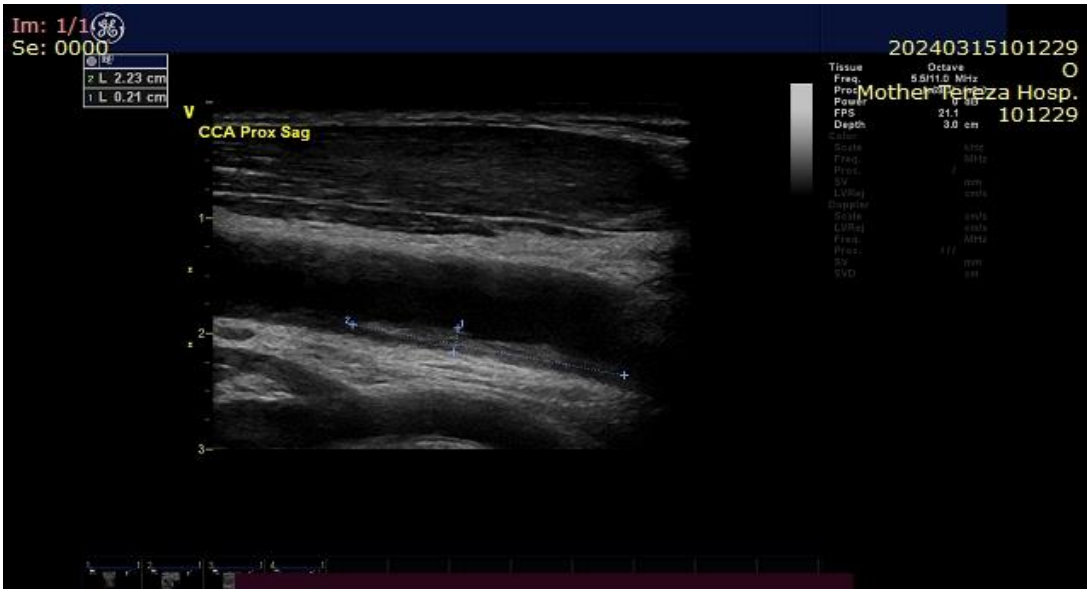


Figure 5. Intima-media thickness (plaque)

The bifurcation is one of the areas most affected by the formation of atherosclerotic plaques, due to the blood flow gaps that are created in this segment.

What is a carotid plaque?
Plaque is made up of deposits of fatty substances, cholesterol, cellular waste products, calcium, and fibrin.

Pathology
The plaques formed in the carotid vessels can be divided into four types:

- type I: predominantly hemorrhage, lipid, cholesterol, and proteinaceous material
- type II: dense fibrous connective tissue with >50% volume of hemorrhage, lipid, cholesterol, and proteinaceous material
- type III: dense fibrous connective tissue with <50% volume of hemorrhage, lipid, cholesterol, and proteinaceous material
- type IV: dense fibrous connective tissue (8)

Ultrasound
On grayscale, characterization of plaques can be performed:

- type I: predominantly hypoechoic with thin echogenic rim
- type II: echogenic plaque with >50% hypoechoic areas
- type III: echogenic plaque with <50% hypoechoic areas
- type IV: uniformly echogenic plaque (8)
- type V: calcified plaque

They can be termed as:

- homogeneous (type I and IV)
- heterogeneous (type II and III) (8)

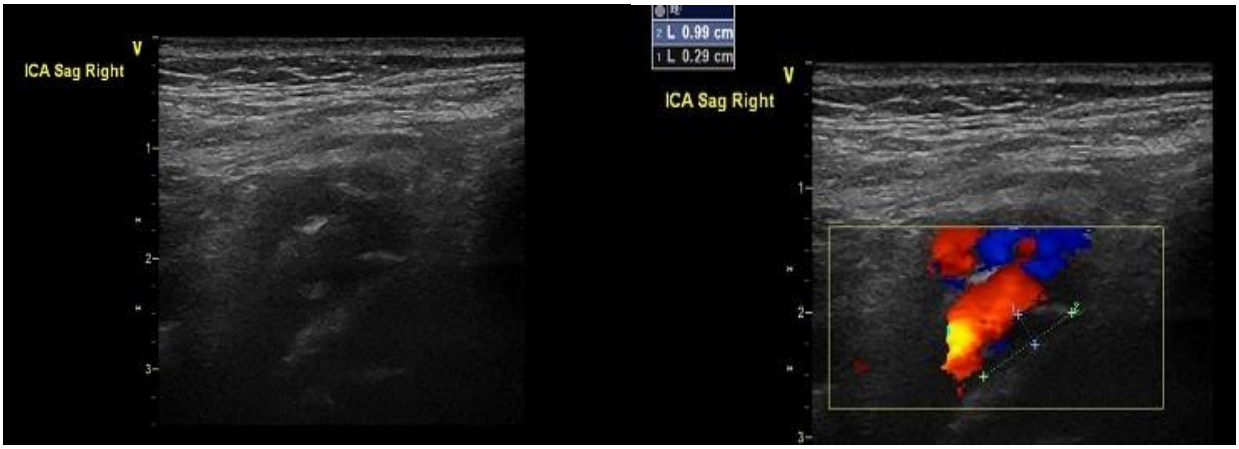


Figure 6. Types I plaque (Grayscale)

Grayscale features that are associated with unstable plaques (plaques at highest risk for rupture and sequela for CVD events) are low grayscale median value, black areas near the lumen surface of the plaque, and the presence of discrete white areas (DWAs) within the plaque (Fig. 6). The size of the plaque (as measured by calculating plaque area [two-dimensional imaging] and volume [three-dimensional imaging]) has also been used to examine associations with CVD risk factors and risk for future CVD event (9).

Several studies have demonstrated that these grayscale features are associated with plaque tissue composition when comparing ultrasound grayscale findings with surgical and histopathology findings post-carotid endarterectomy. Lower GSM values (more hypoechoic) are associated with more lipid content and inflammatory cells. Plaques with higher grayscale median values are associated with a higher percent of calcium. Plaques with black areas (areas of very low echogenicity) near the lumen surface of the plaque are associated with higher ulceration scores by the surgeon at the time of carotid endarterectomy. DWAs are white areas within a plaque (higher grayscale values – typically 126-255) and are not associated with an acoustic shadow. DWAs are thought to represent areas of increased macrophages and/or neoangiogenesis and have been associated with increased inflammation and hemosiderin scores when comparing their presence on ultrasound images to carotid plaque histopathology findings (9).
Plaque grayscale findings have also been shown to be associated with imaging findings of brain infarct, associations with CVD risk factors, and can be predictive of future events.
Plaques with lower GSM values were associated with an increased incidence of cerebral infarction on brain computed tomography examination compared to patients with higher GSM values (9). Studies have also demonstrated that GSM values are lower in patients with diabetes compared to nondiabetic patients (9). In summary, ultrasound plaque grayscale features are associated with histopathologic findings of inflammation, ulceration, hemorrhage, and calcification. Studies have demonstrated that these features, along with clinical history, can be used to risk stratify patients. Research studies have demonstrated that these features (especially plaque area) are associated with CVD risk factors (9).

Carotid artery stenosis

Methods of assessing the degree of stenosis vary depending on the technique and accuracy of the assessment. Angiography has been considered for many years as the most accurate method for evaluating carotid artery stenosis. The two large clinical trials evaluating the benefit of endarterectomy in symptomatic patients (NASCET and ECST) used different methods to measure carotid stenosis although both relied on catheter angiography.

Both the NASCET and ECST trials used angiography and calculated the percentage of stenosis as a ratio of diameters measured from the angiogram (Figure 7). The NASCET method compared the diameter of the residual lumen in the stenosis with the diameter of the normal ICA lumen distal to the bulb. The ECST method compared the residual lumen in the stenosis with an estimate of the diameter of the artery at the point of the stenosis. As the point of maximum stenosis is commonly found within the bulb, the ECST method typically yields a higher value for a stenosis with a given residual lumen than does the NASCET method (10). Duplex ultrasound has been shown to have good correlation with both NASCET and ECST methods of calculating percentage stenosis and with an appropriate choice of diagnostic criteria each has similar sensitivity and specificity (10) as indicated in Fig. 8.

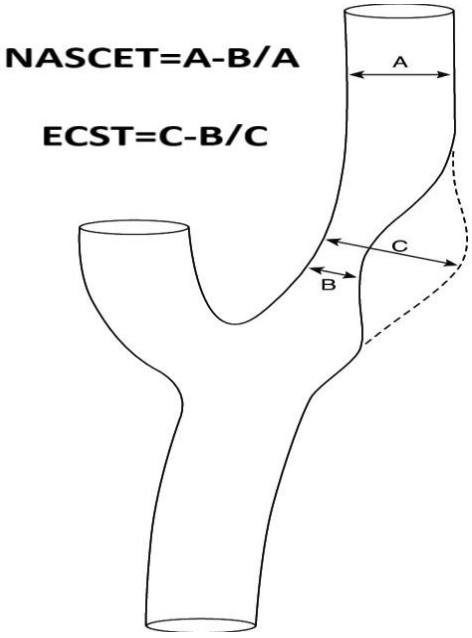


Figure 7. Stenosis measurement (angiography)

Using a regression analysis, Rothwell et al.found the relationship between the ECST and the NASCET values to closely approximate: ECST%=0.6, NASCET%+40% (Figure 8).

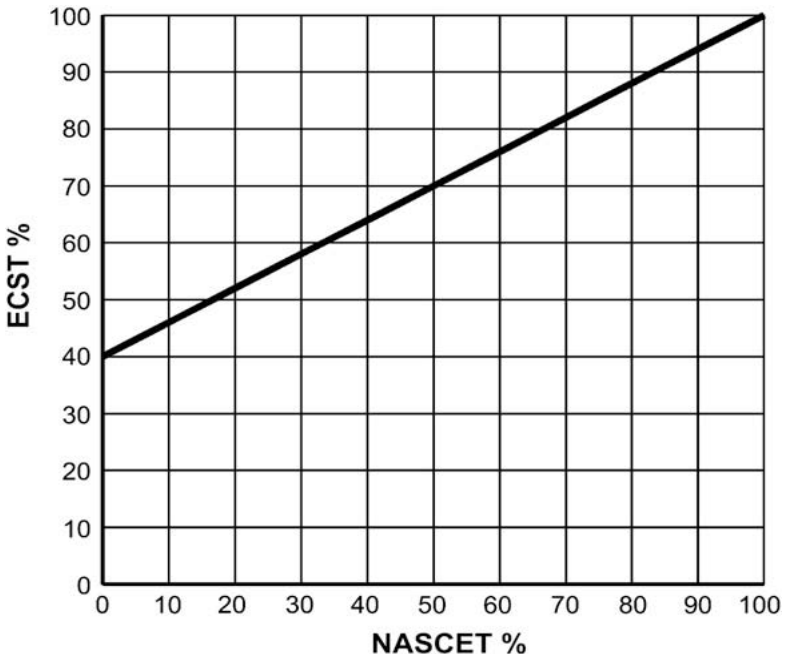


Figure 8. The relationship between percentage diameter stenosis calculated using the ECST and NASCET methods using formula of Rothwell et al. (10)

However, in recent years with the development of biomedical technology, new ways of evaluation and diagnosis have been introduced into the daily routine. The same assessment methodology of Carotid artery stenosis can also be applied in ultrasound and is defined as anatomical stenosis (Figure 9). A complementary method is the measurement of the area of the stenosis. However, due to the low accuracy, such a method is not very advisable (Fig.10).

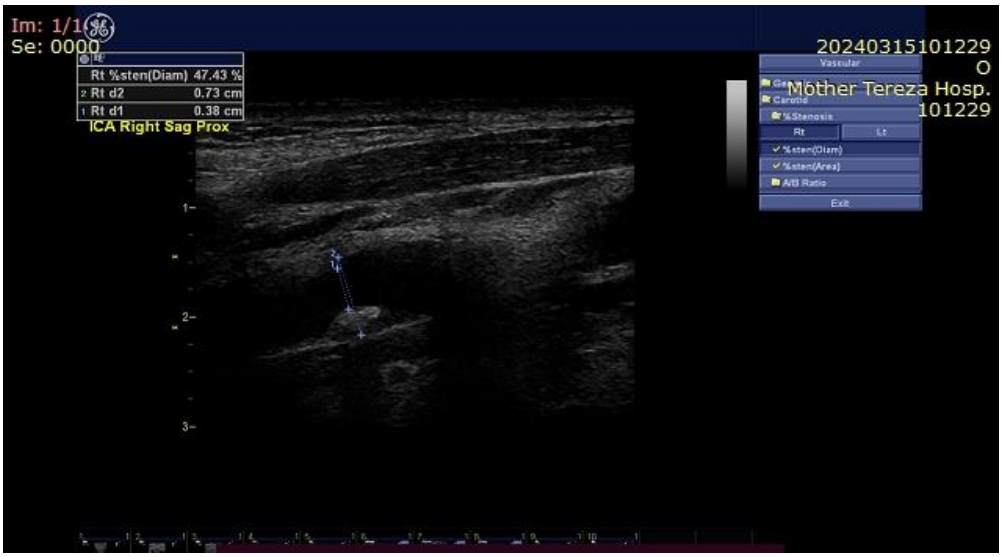


Figure 9. Evaluation of stenosis using diameters (ECST method)

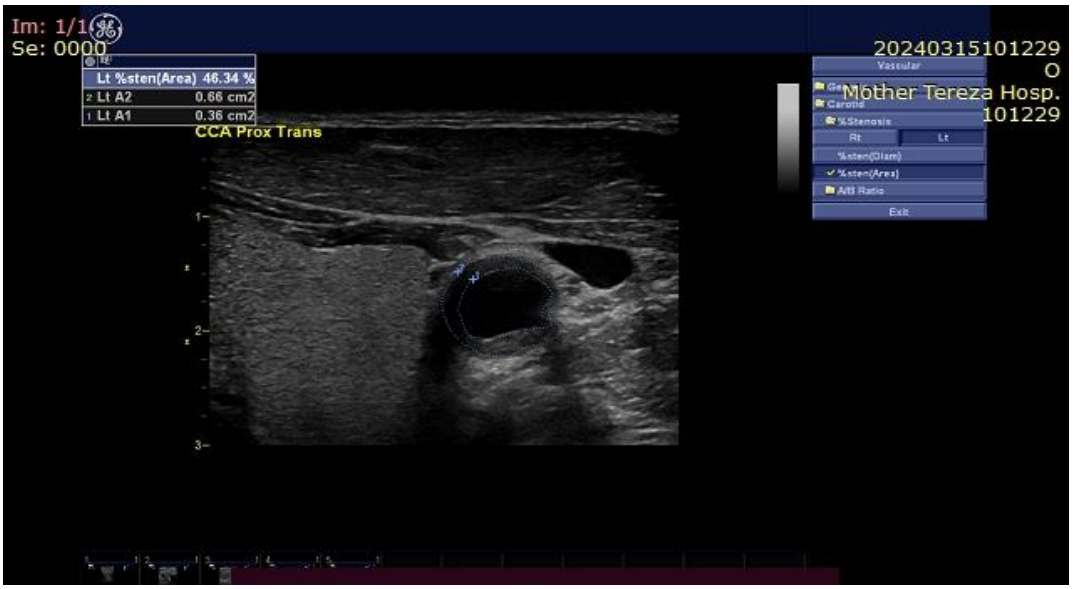
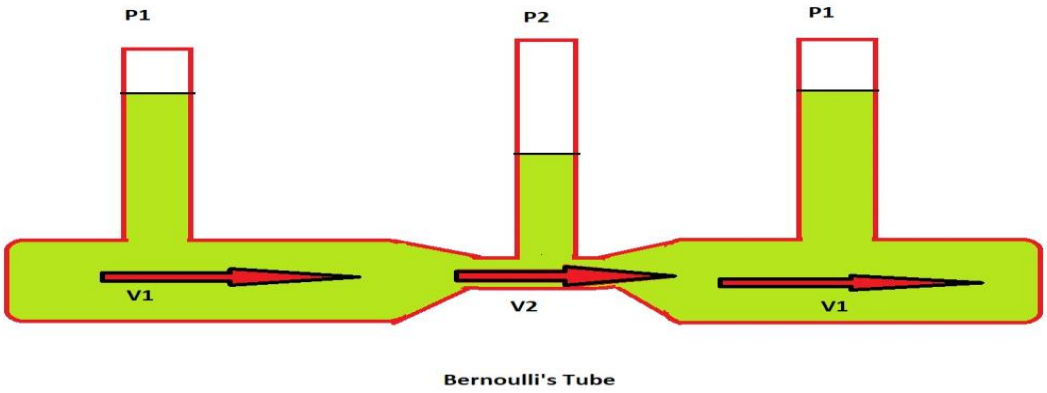


Figure 10. Evaluation of stenosis using area

Using longitudinal plane with colour and spectral Doppler the extracranial carotid arteries should be assessed for any areas for velocity increase or turbulence from the CCA to the distal ICA, and the vertebral artery (11).
Let's recall Bernoulli's principle, which states that: *when the speed of a moving fluid increases, the pressure inside the fluid decreases.* More specifically: the fluid velocity increases in segments with narrowing of the section (Fig. 11).



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igure 11. Bernoulli's tube

This is also the principle on which the evaluation of stenoses (hemodynamic) is based by measuring the speed of blood flow at the point of stenosis. Through various studies and comparison of velocities with measurements made by other methods (angiography, interventional and post-mortem measurements) a direct relationship between the degree of stenosis and the measured velocities has been determined. Haemodynamically significant stenoses are diagnosed by using the standard criteria (5) as shown in the Table 1.

Table 1. Stenosis-grading scheme Internal Carotid Artery (Oates CP et al.) (5)

Stenosis-grading scheme ICA			
Stenosis %	PSV	PSV ratio	St. Mary ratio
NASCET based	PSVICA (cm/s)	PSVICA/PSVCCA	PSVICA/EDVCCA
<50%	<125	<2	<8
50-59%	>125	2-4	8-10
60-69%			11-13
70-79%	>230	>4	14-21
80-89%			22-29
>90%	>400	>5	>30
Near occlusion	High, low or string flow	Variable	Variable
Occlusion	No flow	Not applicable	Not applicable

Velocity measurements should be made at several points: before stenosis, at stenosis and after stenosis (12). To fully enable clinical decisions to be made regarding patient management, it is advisable to define the degree of stenosis within a band of 10%, ranging from 50% to 99% stenosis (10).

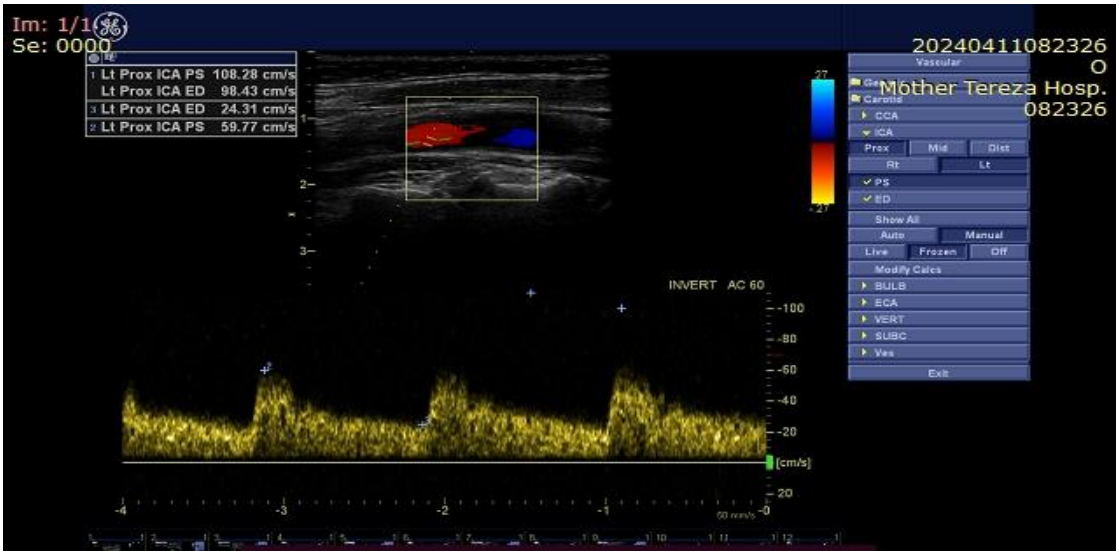


Figure 12. Peak systolic velocity, end diastolic velocity measurement

ICA peak systolic velocity has historically been the primary diagnostic criteria applied to carotid disease (10).
There are a number of potential sources of variability in the internal carotid artery peak systolic velocity. Such factors as:

- variation in the geometry of the bifurcations and the size of bulb
- variation in the vessel size that reflects body size
- collateral flow effects including intracranial/ECA

- collateral flow
- change in ICA flow over the menstrual cycle
- change with age and blood pressure
- the physical parameters of the ultrasound machine (10).

The effect of these factors on blood velocities in diseased vessels is mitigated by the use of velocity ratios. Velocity ratios will also mitigate inter-machine differences (10). The Peak Systolic Velocity Ratio (PSVR), the ratio of the PSV in the ICA to the PSV in the distal CCA, has been widely used (Fig. 12) (10). The St Mary's ratio is formed from the ratio of the PSV in the ICA as the numerator, a value that increases with degree of stenosis, over the EDV in the distal CCA as the denominator, a value that decreases with increasing ICA resistance caused by a progressively severe stenosis. This produces a graph with a wide range of values for the index and sufficiently low data spread so as to allow grading in deciles (10).

New technologies in the evaluation of carotid artery plaques and stenoses

Among diagnostic methods, contrast enhancement ultrasound (CEUS) which uses a contrast medium based on sulfur hexafluoride, has emerged in the last decade as a reliable technique not only due to its ability to quantify the grade of stenosis, but also for its superior capability in depicting the vulnerability features of the plaque, thus providing an accurate qualitative assessment and stratification of the risk of rupture. It also represents a valid method in the evaluation of carotid dissection. CEUS uses an intra-vascular contrast agent consisting of microbubbles (1–8 μm) filled with perfluorinated gas with low solubility injected to acquire high contrast ultrasonic images of the carotid artery. It allows some limitations of DUS to be overcome, such as the detection of low blood flow and insonation of deep vessels (13).

3-D ultrasound

New perspectives are being gained through the 3D technique. While providing a model in three spatial planes, the software provides a read-out of the quantitative analysis of maximum stenosis and plaque volumetric measurement of the plaques; this can be made with a 3D-US system based on 2D-US image acquisition and can be measured accurately and with low variability, making it a useful tool in clinical studies of the progression and regression of carotid plaques (13).

Conclusion

Doppler ultrasound of the carotid arteries is a simple examination, without risks and easily accessible. By correctly recognizing the indications, and correctly evaluating the results of the DUS, the clinician can determine the degree of the patient's cardiovascular risk, the risk of cerebrovascular diseases, determine the medication as well as the indications for surgical intervention in cases of carotid artery stenoses.

Because of the different ways of evaluating and calculating carotid artery stenoses that are in use today, as well as because of changes in lifestyle or life expectancy in different countries, it is recommended that a standard be established for the evaluation of stenoses of the carotid arteries, as well as the stratification of cardiovascular risk based on carotid artery assessments for the Albanian population. The compilation of medical protocols for the determination of risks and treatment by associations and professionals in the field is the need of the hour.

Conflict of interest: None declared.

References

1. Jones J, Hacking C, Glick Y, et al. Common carotid artery. Reference article, Radiopaedia.org (Accessed on 17 Apr 2024)
2. Jones J, Engelbrecht Z, Sheikh Y, et al. Internal carotid artery. Reference article, Radiopaedia.org (Accessed on 17 Apr 2024)
3. Vertebral artery Author: Jana Vasković, MD • Reviewer: Francesca Salvador, MSc
4. Circle of Willis Author: Edwin Ocran • Reviewer: Roberto Grujičić
5. Vascular Technology Professional Performance Guidelines Extracranial Cerebrovascular Duplex Ultrasound Examination (The Society for Vascular Technology of Great Britain and Ireland)
6. UT Southwestern Department of Radiology. Ultrasound - carotid doppler complete evaluation
7. Intima-media thickness: appropriate evaluation and proper measurement. An article from the e-Journal of Cardiology Practice Vol. 13, N° 21 - 05 May 2015Assoc. Prof Iana Simova
8. Di Muzio B, Sharma R, Foo M, et al. Carotid artery stenosis. Reference article, Radiopaedia.org (Accessed on 17 Apr 2024)
9. Grayscale Analisis of Carotid Plaque an Overview Carol Mitchell,PhD, RDMS, RDCS, RVT, RT(R), ACS,
10. Joint Recommendations for Reporting Carotid Ultrasound Investigations in the United Kingdom
11. Vascular Technology Professional Performance Guidelines Extracranial Cerebrovascular Duplex Ultrasound Examination (The Society for Vascular Technology of Great Britain and Ireland)
12. Weerakkody Y, Wahab R, Murphy A, et al. Ultrasound assessment of carotid arterial atherosclerotic disease. Reference article, Radiopaedia.org (Accessed on 17 Apr 2024)
13. Emanuele David, Ombretta Martinelli, Patrizia Pacini, Marco Di Serafino et al. New Technologies in the Assessment of Carotid Stenosis: Beyond the Color-Doppler Ultrasound—High Frame Rate Vector-Flow and 3D Arterial Analysis Ultrasound

THE KEY CHALLENGES OF BIDIRECTIONAL MANAGEMENT OF PATIENTS WITH CANCER AND CHRONIC KIDNEY DISEASE

Matilda Imeraj[1], Enkelejda Çuedari[2], Alba Agaraj[3], Xhuljana Gjini[1], Ernisa Kokomani[1], Eriola Bolleku[1], Alma Idrizi[1]

[1]Service of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania
[2]University Hospital Center "Mother Teresa", Service of Oncology, Tirana, Albania
[3]Department of Public Health, Faculty of Medicine, University of Medicine, Tirana, Albania

Correspondent E-mail : imerajmatilda@hotmail.com

Abstract

Chronic kidney disease is a significant growing health problem, with prevalence of 9.1%–13.4% of the population worldwide. Cancer is the second leading cause of death in people with chronic kidney disease. The incidence of chronic kidney disease in patients with cancer is higher than in the non-cancer population and is associated with reduced cancer survival.

Chronic kidney disease can complicate cancer treatment due to impaired kidney function, which affects drug metabolism and clearance. Chemotherapy drugs and other medications may need to be adjusted to minimize the risk of toxicity and maintain efficacy. Managing cancer in patients with kidney disease, including those undergoing dialysis, requires a sensitive approach due to the impact of both conditions. In this review, we aim to highlight the crucial role of multidisciplinary approach that requires a strict comprehensive understanding of treatment options to provide optimal care and improve patient outcomes.

Keywords: Cancer, Chronic kidney disease, Anticancer therapy, Management.

SFIDAT KRYESORE TË MENAXHIMIT BIDIREKSIONAL TË PACIENTËVE ME KANCER DHE SËMUNDJE KRONIKE TË VESHKAVE

Abstrakt

Sëmundja kronike e veshkave është një problem i rëndësishëm ne sistemin shëndetësor, me prevalencë prej 9,1%-13,4% të popullsisë në mbarë botën. Kanceri është shkaku i dytë kryesor i vdekjeve tek njerëzit me sëmundje kronike të veshkave. Incidenca e saj në pacientët me kancer është më e lartë se në popullatën normale dhe shoqërohet me ulje të mbijetesës së kancerit.

Sëmundja kronike e veshkave mund të komplikojë trajtimin e kancerit për shkak të funksionit të dëmtuar të veshkave, i cili ndikon në metabolizmin dhe pastrimin e barnave. Barnat e kimioterapisë dhe medikamentet e tjera mund të kenë nevojë të modulohen ne doza për të minimizuar rrezikun e toksicitetit dhe për të ruajtur efikasitetin. Menaxhimi i kancerit në pacientët me sëmundje të veshkave, duke përfshirë ata që i nënshtrohen dializës, kërkon një qasje

të ndjeshme për shkak të ndikimit të të dy kushteve. Si përfundim, në këtë permbledhje, ne synojmë të theksojmë rolin vendimtar të qasjes multidisiplinare që kërkon një kuptim të rreptë gjithëpërfshirës të opsioneve të trajtimit për të ofruar kujdes optimal dhe për të përmirësuar rezultatet e pacientit.

Fjalë kyçe: Kanceri, Sëmundja renale kronike, Terapia kundër kancerit, Menaxhimi.

Introduction

Chronic kidney disease (CKD) affects more than 10% of the general population worldwide, amounting to >800 million individuals (1). Bidirectional relationship between CKD and other conditions is essential to improve the outcomes among these enormous number of patients. Many studies have revealed that the incidence of CKD in cancer patients is higher than in general population. Understanding this crucial relationship can affect in treatment options, quality of life and survival. It's important to underline the potential benefits of recognizing increased risk of cancer in risk prediction mechanisms used for the management of CKD and vice versa.

1.1 CKD and incident cancer

There is an increased risk of cancer incidence and death associated with kidney function (2). In a French observational study The Renal Insufficiency and Cancer Medications (IRMA) of nearly 5000 patients approximately half of participants diagnosed with cancer had mild reduction in kidney function (3), demonstrating the high prevalence of renal impairment.

In a prospective cohort study in Taiwan with 405878 participants, with major chronic diseases, CKD contributed to more than one fifth of the risk for incident cancer and more than one third of the risk for cancer death (4).

The link of low estimated glomerular filtration rate (e-GFR) and albuminuria is well known and are commonly associated with cancer risk. Various studies demonstrate that there is an increased risk of incident cancer in patients with albuminuria (5).

1.2 The role of e-GFR in incident cancer

According to Kidney Disease Improving Global Outcomes (KDIGO), CKD is defined as abnormalities of kidney structure or function present (GFR) < 60 mL/1.73 m2 for 3 months or more, irrespective of cause and is classified based on causes, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA. Several studies have shown a potential relationship between markers of CKD (below eGFR 60 ml/min/1.73m2, with or without albuminuria) with higher risk of incidence from overall cancers (6-8). Despite the contradictions of kidney function assessment, e-GFR should be calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine (e-GFRcr), cystatin C (e-GFR-cys) or a combination of creatinine and cystatin C (e-GFRcr-cys) (9). Cancer incidence and mortality may be detectable early in CKD, and is more easily detected using e-GFR-cys (10). The impact of CKD markers is crucial on cancer outcome in particular is concerning and needs special consideration (11).

2. Potential mechanisms of CKD and cancer connections

The potential mechanisms of CKD-associated cancer or anticancer therapy-associated kidney injury remain profoundly in decipherable, although in recent years, the link has been well established and there has been rapid advancement in this interdisciplinary approach.

Increased cancer incidence rate in CKD might be due to chronic inflammation, accumulation of carcinogenic compounds, oxidative stress, impairment of DNA repair, excessive parathyroid hormone and changes in intestinal microbiota (12-15). Persistent low-grade inflammation had been identified as an important pathological trait of CKD. The inflammatory condition of CKD is multifactorial, including increased sensitivity to infection, acidosis and oxidative stress, metabolic changes of adipose tissue and intestinal conditions (12, 13). Biomarkers of inflammation (IL-1β, IL-6, and TNF-α) are inversely associated with measures of kidney function. It is well established that chronic inflammation is one of the common peculiarity of infections. Analogously, inflammation has long been considered as one of the important participants in the process of cancer formation leading to tumor growth, invasion and metastasis. Radical oxygen scavengers (ROS) is constantly generated by aerobic metabolism mitochondria (15), during oxidative stress, this causes serious damage to cell structure and function and induce mutations and cancer cells transformations.

In CKD patients, low DNA damage repair capacity may lead to mutable genes and aberrations in the chromosome, which might be responsible for pathological transformations of cells (16, 17).

Many studies approve that end stage kidney disease patients have uremic environment and are exposed to high levels of carcinogenic compounds due to reduction of excretion and accumulation of such substances in plasma. Progression of CKD causes decline of renal function and this leads to hypocalcemia and hyperphosphatemia and is the main cause of hyperparathyroidism. It has been reported that this condition might be pro-carcinogenic (18, 19).

3. Anticancer treatments and acute kidney injury / chronic kidney disease

Many studies confirm that anticancer therapy, including chemotherapy, radiotherapy, nephrectomy, molecular targeted therapy and immune checkpoint inhibitor cause acute kidney injury (AKI)/proteinuria and hypertension (20, 21).

Some of these treatments are cleared by the kidney or may have nephrotoxicity (22). Limiting patient access to best treatment options solely because of the presence of kidney disease is a form of renalism. The renalism was first used almost two decades ago by Chertow et al., to depict the systematic withholding of indicated, potentially beneficial studies and interventions from patients on the basis of coexisting kidney disease (23).

Platinum, crizotinib, ifosfamide typically cause tubular disfunction, the risk of renal side effects increases with higher doses and cumulative exposure, co-administration with other therapies and in patients with pre-existing kidney disease (24, 25). Thrombotic microangiopathy is a common side effect of gemcitabine and antiangiogenetic drugs and BRAF inhibitors/tyrosine kinase inhibitors are well known for the tubulointerstitial injury (26).

Studies estimate that approximately 50% of patients with cancer have decreased kidney function and receive at least one anticancer drug that requires dose adjustment, which may influence treatment decisions and overall management.

3.1 Medications use in the treatment of CKD may cause cancer

Erythropoiesis-stimulating agents, used in the treatment of renal anaemia, may exacerbate pre-existing cancers (27). Glomerulonephritis treatments algorithm include some medications (such as cyclophosphamide) and it is proved that can increase the risk of certain cancer (24).

4**. Cancer in dialysis and kidney transplanted patients**

Cancers occurring after dialysis or transplantion have long been described, but risk assessment by cancer site has been available only recently. Cancers most strongly associated with dialysis include tumors of the oral cavity (Kaposi sarcoma), kidney, bladder, thyroid, lung, liver and cervix (28-30). Dialysis patients are at risk of fluid and electrolyte imbalances, which can be exacerbated during cancer treatment. Careful observation of fluid status, electrolyte levels, and kidney function is mandatory to prevent complications such as hyperkalemia, fluid overload, and electrolyte disturbances (31). Kidney transplant patients are excluded in most clinical trials but few randomized controlled trials oriented for skin or other conditions due to the nature of being on immunosuppressive agents and the resulting complexities of treatment protocol. Kidney transplant recipients are at very high risk of cancers (32-34), most, but not all, of which with likely viral (Epstein–Barr virus, cytomegalovirus, human papillomavirus, human T-cell lymphotropic virus and hepatitis B and C) etiology (35).

Conclusion

CKD is common in cancer and it is related with high incidence and mortality rate among these patients. The risk is under-recognized due to the fact that most clinical trials exclude these subgroups and kidney function markers such as e-GFR and albuminuria are not acknowledged in cancer risk calculators. Kidney markers of glomerular filtration like cystatin C reveal an association with increased risk of cancer incidence and mortality at an earlier stage.

Accurate measurement or estimation of kidney function is vital to appropriate anticancer therapy dosing. A limpid understanding of the mechanisms will aid in devising strategies to reduce cancer risk among people with CKD. Identifying the causative drug and stopping exposure in acute toxic injury or detecting and treating chronic kidney injury as early as possible it is now considered the best way in managing CKD-Cancer patients. Multidisciplinary approach is mandatory to fill the knowledge gap and improve the outcome of cancer patients with kidney dysfunction.

Conflicts of Interest: No conflict of interest.

References

1. Jager K.J., Kovesdy C., Langham R., et al. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019;96:1048–1050

2. Lees JS, Ho F, Parra-Soto S et al. Kidney function and cancer risk: an analysis using creatinine and cystatin C in a cohort study. EClinicalMedicine 2021; 38: 101030.
3. Tu H, Wen CP, Tsai SP et al. Cancer risk associated with chronic diseases and disease markers: prospective cohort study. BMJ 2018; 360: k134. doi: 10.1136/bmj.k134
4. Weng PH, Hung KY, Huang HL et al. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. Clin J Am Soc Nephrol.2011; 6: 1121–1128
5. Mok Y, Matsushita K, Sang Y et al. Association of kidney disease measures with cause-specific mortality: the Korean Heart Study. PLoS One 2016; 11: e0153429.
6. Liu L., Zhu M., Meng Q. Association between kidney function and the risk of cancer: results from the China health and retirement longitudinal study (CHARLS) J Cancer. 2020;11:6429–6436.
7. Mok Y., Ballew S.H., Sang Y. Albuminuria, kidney function, and cancer risk in the community. Am J Epidemiol. 2020;189:942–950.
8. Tu H., Wen C.P., Tsai S.P. Cancer risk associated with chronic diseases and disease markers: prospective cohort study. BMJ. 2018;360:k134.
9. Inker L.A., Schmid C.H., Tighiouart H. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–29.
10. Putri, A. Y., and Thaha, M. (2014). Role of Oxidative Stress on Chronic Kidney Disease Progression. Acta Med. Indones. 46, 244–252.
11. Lees JS, Ho F, Parra-Soto, S et al. Kidney function and cancer risk: an analysis using creatinine and cystatin C in a cohort study. EclinicalMedicine.2021;38: 101030.
12. Dai, L., Golembiewska, E., Lindholm, B., and Stenvinkel, P. (2017). “End-Stage Renal Disease, Inflammation and Cardiovascular Outcomes,” in Expanded Hemodialysis: Innovative Clinical Approach in Dialysis, 32–43. doi:10.1159/000479254
13. De Cavanagh, E. M. V., Piotrkowski, B., and Fraga, C. G. (2004). Concerted Action of the Renin-Angiotensin System, Mitochondria, and Antioxidant Defenses in Aging. Mol. Aspects Med. 25, 27–36. doi:10.1016/j.mam.2004.02.006
14. Ebert, T., Pawelzik, S.-C., Witasp, A., Arefin, S., Hobson, S., Kublickiene, K., et al. (2020). Inflammation and Premature Ageing in Chronic Kidney Disease. Toxins 12, 227. doi:10.3390/toxins12040227
15. Masereeuw, R., Mutsaers, H. A. M., Toyohara, T., Abe, T., Jhawar, S., Sweet, D. H., et al. (2014). The Kidney and Uremic Toxin Removal: Glomerulus or Tubule? Seminars Nephrol.34, 191–208. doi:10.1016/j.semnephrol.2014.02.010
16. De Cavanagh, E. M. V., Piotrkowski, B., and Fraga, C. G. (2004). Concerted Action of the Renin-Angiotensin System, Mitochondria, and Antioxidant Defenses in Aging. Mol. Aspects Med. 25, 27–36. doi:10.1016/j.mam.2004.02.006
17. Sevilya, Z., Leitner-Dagan, Y., Pinchev, M., Kremer, R., Elinger, D., Rennert, H. S., et al. (2014). Low Integrated DNA Repair Score and Lung Cancer Risk. Cancer Prev. Res. 7, 398–406. doi:10.1158/1940-6207.CAPR-13-0318
18. Lau, W. L., Obi, Y., and Kalantar-Zadeh, K. (2018). Parathyroidectomy in the Management of Secondary Hyperparathyroidism. Clin. J. Am. Soc. Nephrol. 13, 952–961.
19. Lavi-Moshayoff, V., Wasserman, G., Meir, T., Silver, J., and Naveh-Many, T. (2010). PTH Increases FGF23 Gene Expression and Mediates the High-FGF23 Levels of

Experimental Kidney Failure: a Bone Parathyroid Feedback Loop. Am. J. Physiology-Renal Physiology 299, F882–F889. doi:10.1152/ajprenal.00360.2010
20. De Francisco, A. L. M., Macía, M., Alonso, F., García, P., Gutierrez, E., Quintana, L. F., et al. (2019). Onco-Nefrología: Cáncer, Quimioterapia Y Riñón. Nefrología 39, 473–481. doi:10.1016/j.nefro.2018.10.016
21. Ding, H., Wu, X., and Gao, W. (2005). PD-L1 Is Expressed by Human Renal Tubular Epithelial Cells and Suppresses T Cell Cytokine Synthesis. Clin. Immunol. 115, 184–191. doi:10.1016/j.clim.2005.01.005.
22. Burtrovich MA Reaves AC Heyward J, et al. Inclusion of participants with CKD and other kidney-related considerations during clinical drug development: landscape analysis of anticancer agents approved from 2015-2019. Clin J Am Soc Nephrol. 2023;18(4):455–464.
23. Chertow GM, Normand SL, McNeil BJ. "Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. J Am Soc Nephrol.2004;15(9):2462–246
24. Bitran JD, Desser RK, Billings AA, Kozloff MF, Shapiro CM. Acute nephrotoxicity following cis-dichlorodiammine-platinum. Cancer. 1982;49:1784-1788.
25. Santos MLC, Brito BB, da Silva FAF, Botelho ACDS, Melo FF. Nephrotoxicity in cancer treatment: An overview. World J Clin Oncol 2020; 11(4): 190-204.
26. Hauschild A, Grob JJ, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380:358-365.
27. Magee C. Kidney disease and death from cancer. Am J Kidney Dis.2014; 63: 7–9.
28. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. Jama. 2006;296:2823–2831.
29. Cosmai, L., Porta, C., Gallieni, M., and Perazella, M. A. (2016). Onco-nephrology: a Decalogue: Table 1. Nephrol. Dial. Transpl. 31, 515–519. doi:10.1093/ndt/gfv320
30. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients-where do we stand today? Am J Transplant. 2008;8:2192–2198.
31. Rosner M. Daikin A et al. Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clin J Am Soc Nephrol. 2012; 7: 1722-1729.
32. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant. 2007;7:941–948.
33. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation Transplantation. 2005;80 (Suppl):S254–264.
34. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004;4:905–913.
35. Van Leeuwen MT, Webster AC, McCredie MRE et al. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ 2010; 340: c570.

PRINCIPLES OF HEART FAILURE TREATMENT

Somida Kuka, Eneida Hoxha, Sonil Marku, Margarita Gjata Resuli.
Internal Medicine and Hypertension Service,
University Hospital Center "Mother Teresa" Tirana, Albania.

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

Abstract

Introduction: Heart Failure is a complex syndrome that arises as a severe complication of various cardiac disorders. It is characterized by high mortality rates, akin to those seen in malignant diseases. It is categorized based on cardiac function into two main types: Heart Failure with preserved ejection fraction and Heart Failure with reduced ejection fraction. The latter is further subdivided into mild and severe reductions in function. Common clinical manifestations include dyspnea, peripheral edema, and fatigue. The etiology of Heart Failure may include ischemic, valvular, and myocarditis-related origins, among others influenced by factors such as post-tachycardia, pharmaceutical interactions, alcohol use, etc. The functional classification remains a crucial aspect of understanding and managing the disease.

Objectives: Given the severity of Heart Failure, it is imperative to manage the underlying causes effectively to prevent its onset. Lifestyle modifications and addressing modifiable risk factors are vital in thwarting the progression of this syndrome. In established cases, optimizing treatment strategies is essential to enhance survival rates and improve quality of life.

Materials and Methods: This paper draws on recent studies that explore innovative therapeutic approaches for heart failure, reflecting a significant body of ongoing research aimed at improving patient outcomes.

Conclusion: Effective management of Heart Failure involves recognizing and mitigating the risk factors that contribute to its development. Accurate diagnosis and appropriate treatment of cardiac pathologies are crucial. Furthermore, adopting newer treatment modalities is essential for the effective management of Heart Failure cases, aiming to prolong life and enhance its quality.

Keywords: syndrome, function, heart failure.

PARIMET E MJEKIMIT TË INSUFICIENCËS KARDIAKE

Abstrakt

Hyrje: Insuficienca kardiake është një patologji komplekse që vjen si ndërlikim i rëndë i sëmundjeve të ndryshme kardiake. Karakterizohet nga një shkallë e lartë vdekshmërie njëlloj si e patologjive malinje. Ajo klasifikohet mbështetur ne funksionin kardiak në dy lloje: Në Insuficiencën kardiake me fraksion ejeksioni të ruajtur dhe në Insuficiencën kardiake me fraksion ejeksioni të reduktuar. Ky i fundit nën-ndahet në variantin me reduktim të lehtë të fraksionit të ejeksionit dhe në variantin me reduktim sever të fraksionit të ejeksionit. Manifestimet klinike më të zakonshme përfshijnë dispnenë, edemat periferike dhe lodhjen. Etiologjia e Insuficiencës kardiake kongjestive mund të jetë me origjinë iskemike, valvular dhe nga miokarditi, dhe ndër të tjera mund të ndikohet nga faktorë si p.sh. post-takikardia, ndërveprimet medikamentoze, përdorimi i alkoolit etj. Klasifikimi funksional mbetet pika kyçe e kuptimit dhe trajtimit të kësaj patologjie.

Objektivat: Duke patur parasysh gravitetin e Insuficiencës kardiake, është e detyrueshme të trajtohen shkaqet që do të sillnin shpërthimin e klinikës së kësaj patologjie. Modifikimi i stilit të jetesës dhe ndikimi në faktoret e riskut të ndryshueshëm janë vitale për të penguar evolucionin e kësaj patologjie. Në rastet e stabilizuara optimizimi i strategjive terapeutike rrit mbijetesën dhe cilësinë e jetës së këtyre pacientëve.
Materialet dhe metodat: Ky punim prezanton një përmbledhje të studimeve të fundit që eksplorojnë përqasjet e reja dhe novative terapeutike të trajtimit të Insuficiencës kardiake kongjestive duke reflektuar studimet që po kryhen për të përmirësuar cilësinë e jetës së pacientëve.
Konkluzione: Trajtimi efikas i Insuficiences kardiake përfshin njohjen dhe eliminimin e faktorëve që do të kontribuonin në zhvillimin e saj. Diagnoza e kujdesshme dhe trajtimi i duhur i patologjive kardiake eshte thelbësor. Gjithashtu, adaptimi i modaliteteve të reja terapeutike është esencial për manaxhimin efikas të Insuficiencës kardiake kongjestive, duke synuar në zgjatjen e jetës dhe në përmirësimin e cilësisë së saj.

Fjalët kyç: sindromë, funksion, Insuficienca kardiake kongjestive

Introduction

Heart failure is a complex syndrome that is accompanied by the inability of the cardiac muscle to deliver sufficient blood flow to the body's vascularization. The American College of Cardiology Foundation (ACCF) / as well as the Heart Association (AHA) guidelines define Cardiac Insufficiency (CI) as a complex clinical syndrome, the result of structural and/or functional impairment of ventricular filling and ejection, which leads to the cardinal clinical symptoms of dyspnea and fatigue as well as signs of HF (respectively oedema and rales, etc.) (1). HF is a growing problem worldwide. The overall prevalence of HF in the adult population in developed countries is 2% (2). The prevalence follows an exponential pattern, increasing with age, and affects 6–10% of people aged > 65 (2). The etiology is numerous: ischemic, valvular, idiopathic, alcoholic, medicinal (antitumoral), metabolic, toxic, etc. HF is divided into two large groups: HF with preserved EF and HF with reduced EF. Clinical signs are: difficulty in breathing, general weakness, decreased diuresis, peripheral oedema, abdominal discomfort (from liquid), arrhythmia, etc.

Pathogenesis

HF is a progressive disorder that begins after an event or injury to the heart muscle that results in a functional loss of cardiac myocytes, or otherwise, impairs the ability of the myocardium to generate force, thereby making it impossible for the heart to contract normaly. This event may have a sudden onset, as in the case of an MI; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overload. Regardless of the nature of the event, the feature that is common to each of these events is that they all in some way produce a decrease in pumping capacity. Although the exact reasons why patients with left ventricular (LV) dysfunction may remain asymptomatic are not known, one possible explanation is that a variety of compensatory mechanisms are activated in the presence of an injured heart and/or LV dysfunction allowing patients to maintain and modulate LV function for a period of several months to several years (1). Compensatory mechanisms that have been described so far include: (a) activation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic nervous

system, which are responsible, respectively, for maintaining cardiac output through increased salt and water retention and (b) increased myocardial contractility. In addition, a family of antagonistic vasodilator molecules are activated, including atrial and brain natriuretic peptides (ANP and BNP), bradykinin, prostaglandins (PGE2 and PGI2), and nitric oxide (NO), which compensate for excessive peripheral vascular vasoconstriction. These compensatory mechanisms can modulate LV function within a physiological range. Thus, patients may remain asymptomatic or minimally symptomatic for years; however, at some point patients become markedly symptomatic. Although the exact mechanisms responsible for this transition are not known, the transition to symptomatic HF is associated with increased activation of the neurohormonal, adrenergic, and cytokine systems leading to a series of adaptive changes within the myocardium referred to as LV remodelling. Although diastolic dysfunction (see below) was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function, etc. The principles of HF treatment are based on these mechanisms. Which are divided into two groups: drug therapy and self-care (2). Drug Therapy: The last 50 years have witnessed great advances in the management of HFrEF. The treatment of symptomatic heart failure evolved from a diuretic and hemodynamic (digoxin, inotropic therapy) model of therapy to the era of disease-modifying therapy with neurohormonal antagonism. In this regard, RAAS inhibitors and beta-blockers form the cornerstone of pharmacotherapy that lead to the improvement of cardiac structure and function, with a reduction in symptoms, a reduction in hospitalizations and a decrease in mortality from Heart Failure and its clinical manifestations. Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combined endpoint of mortality and hospitalizations for HF in patients treated with Angiotensin-converting enzyme inhibitor (ACE-I). Patients treated with beta-blockers provide a further 35% reduction in mortality on top of the benefit provided by ACE-I alone. Increased experience with both agents in a wide range of patients with HFrEF has demonstrated the safety of ACEIs in the treatment of patients with mild renal insufficiency and the tolerability of beta-blockers in patients with moderately controlled diabetes, asthma, and obstructive pulmonary disease. The benefits of ACE-I and beta-blockers extend to advanced disease symptoms (NYHA Class IIIb–IV). However, a significant number of patients with advanced heart failure may not be able to achieve optimal doses of neurohormonal inhibitors and require careful reduction of dose exposure to maintain clinical stability. Based on the investigations, the use of beta-blockers in HFrEF should ideally be limited to carvedilol, nebivolol, bisoprolol and metoprolol succinate – tested and proven agents that improve survival in clinical trials (3).

Beta blockers: The group of beta blockers is used in to counteract the harmful effects of catecholamines produced by activation of the sympathetic nervous system, reducing the heart's need for oxygen as well as exhibiting antiarrhythmic effects. This group has been seen in various studies that increases the life expectancy of patients (15). Depending on the type and aggressiveness of the arrhythmias, more powerful antiarrhythmics such as Amiodarone can be used. From the group of beta-blockers used in HF with reduced EF are Carvedilol, Bisoprolol, Metoprolol and Nebivolol.

Ivabradine slows the heart rate without a negative inotropic effect. Ivabradine is FDA-indicated to reduce the risk of hospitalization, exacerbation in patients with chronic, symptomatic heart failure with a left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute, and or are in maximum tolerable doses of beta-blockers or have a

contraindication for the use of beta-blockers. Ivabradine reduced hospitalizations and death related to cardiovascular disease and HF (18).

ACEI: The ACEI group is very important in the treatment of HF. It works by inhibiting the renin-angiotensin system, through inhibition of the converting enzyme. In this way, the conversion of angiotensin to angiotensin II is inhibited and by further inhibiting the harmful effects of the activation of this system, which are the retention of water and salt in the body, the increase in arterial pressure, the further increase of the sympathetic system, hypertrophy, proliferation, etc (4).

Angiotensin receptor blockers ARBs: The ARBs group acts on the same system as ACE, i.e., the renin-angiotensin-aldosterone system, but the link of their action is at the level of angiotensin II receptors, so they are more specific than ACE in the action of theirs. Here we can mention valsartan, losartan, olmesartan, ibersartan, telmisartan etc (4).

ARNI (sacubitril/valsartan): This drug was approved by the FDA in 2015 for the treatment of HF and consists of sacubitril, which is a niprelysin inhibitor, and valsartan, which belongs to the group of ARBs. Niprelysin is an enzyme that participates in the degradation of natriuretic peptides. By inhibiting niprelysin, sacubitril increases the level of natriuretic peptides that in HF have a positive effect by promoting diuresis and natriuresis. Here is added the positive effect of valsartan as an inhibitor of angiotensin receptors, counteracting the harmful effects of the activation of the angiotensin renin system. Both medications act on HF by potentiating each other's action (8).

Regarding the three groups mentioned above: ACEI, ARBs and ARNI, one of them is used in the treatment of HF. All three or two groups cannot be used together (4).

Aldosterone antagonists: from the name itself, their curative action appears by counteracting the harmful effects of aldosterone (8). Aldosterone antagonism is associated with a reduction in mortality in all stages of NYHA class II to IV symptomatic HFrEF. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, endothelial dysfunction, and may directly contribute to myocardial fibrosis. The selective agent eplerenone (tested in NYHA class II heart failure and after myocardial infarction) and the nonselective antagonist spironolactone (tested in NYHA class III and IV heart failure) reduce mortality and hospitalizations, with significant reductions in sudden death cardiac (9).

A new and very promising group in the treatment of HF is the group of Sodium-glucose Cotransporter-2 (SGLT2) inhibitors. This group acts by inhibiting the renal reabsorption of glucose and promoting diuresis. A positive effect on the myocardium from toxic effects and on cardiac remodelling has also been seen (1, 3).
Loop diuretics: these drugs act on the kidneys by promoting natriuresis and diuresis. The group of these medications has an effect on the clinical improvement of symptoms. Here we mention: Furosemide, Torasemide, etc. Neurohormonal activation results in salt and water retention.
Clinical trial data confirming efficacy are limited and no data suggest that these agents improve survival. Thus, diuretic agents should ideally be used in tailored programs to avoid overexposure. Indeed, diuretics are essential early on to achieve volume control before neurohormonal therapy is well tolerated or titrated (8, 9).

Digitalis (Digoxin) is used in HF that is usually associated with AF to decrease the heart rate and for the positive chronotropic effect. The latter is preferred in HF NYHA IV and significantly reduced cardiac function, even when the patient is with SR. Digitalis exert a mild inotropic effect, soften the baroreceptor activity of the carotid sinus and are sympatho-inhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. Trials showed a reduction in hospitalizations for HF in the treatment group (patients with heart failure and sinus rhythm), but no reduction in mortality. It should be noted that low doses of digoxin are sufficient to achieve a potentially beneficial result, and higher doses violate the index of therapeutic safety. In general, the use of digoxin is now reduced as therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control (1, 2, 4, 6).

A combination of hydralazine with nitrates can be used as additional therapy. Vericiguat is a new drug in the treatment of HF, experience with which is still small (14). ICD/Cordaron are used to prevent life-threatening ventricular arrhythmias, which in these subjects are frequent and constitute the main cause of death (6). In addition to drug therapy, based on the patient's clinical condition, supportive treatment, as well as oxygen therapy, is of particular importance in the advanced stages of HF. In individuals with advanced stages, which is characterized by refractoriness to conventional therapy and with an increased burden of symptoms, frequent hospitalizations, poor quality of life and high risk of death, surgical options remain open. Cardiac Transplant, Circulation Assisted Left Ventricular Assist Systems (LVAS) (7).

It is very important to take good care of yourself.

- A healthy diet, balanced diet can help to improve symptoms and overall health. A balanced diet should include lots of fruit and vegetables, controlled amount of protein, low levels of fat, salt, and sugar. Regular physical activity can also help improve your symptoms and overall health. These patients need physical activity adjusted according to the NYHA scale, education, emotional support (13).
- Stop smoking can improve your overall health and reduce your risk of many other health problems.
- Limit alcohol consumption: In patients with HF, drinking a glass of wine may be allowed, but it is advised not to exceed the recommended limits of more than 14 units of alcohol per week. If HF is directly related to alcohol consumption, you may be advised to stop altogether (12).
- Vaccination in patients with HF is a condition that makes you more vulnerable to infections. Community-acquired respiratory infections are a common cause of hospital readmission in these patients and are associated with an increased risk of in-hospital mortality. Recent studies have shown that vaccination against common respiratory tract infections can reduce hospitalization in patients with HF. For example, in the PARADIGM-HF study, influenza vaccination was associated with a 19% reduction in all-cause mortality (in participants with HFrEF). Likewise, a community-based study of more than 140,000 Heart Failure patients also reported a 19% reduction in hospital readmissions in elderly patients who were vaccinated. It is now widely recommended that patients with Heart Failure be vaccinated annually against influenza, unless contraindicated. In addition, pneumococcal vaccination is also recommended for high-risk patients, including those with diabetes and/or CKD (10).
- Regular rechecking and monitoring. Patients with HF should monitor their condition at least every 6 months.

Conclusion

Heart failure (HF) remains a significant clinical and public health issue due to its complex pathophysiology and high prevalence, especially among the elderly. It emerges primarily from the progressive loss of cardiac myocyte function and subsequent myocardial remodeling processes. Modern therapeutic strategies have significantly evolved from basic symptom management to complex disease-modifying approaches, particularly through neurohormonal antagonism, which substantially improves patient outcomes. These advancements underscore the necessity for continuous medication optimization and the potential integration of new pharmacological agents like ARNI and SGLT2 inhibitors, which show promise in further reducing HF-related morbidity and mortality. Additionally, the role of lifestyle modifications and routine monitoring cannot be overstated, as these are crucial for managing HF symptoms and improving overall patient quality of life. As we continue to witness innovations in heart failure management, the integration of emerging drugs and tailored therapies offers a hopeful outlook for reducing the global burden of this challenging disease.

References

1. Ahmad Malik; Daniel Brito; Sarosh Vaqar; Lovely Chhabra; Congestive Heart Failure: November 5, 2023.
2. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: executive summary: a report of the American College of Cardiology. Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761.
3. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348:2007-2018.
4. Ramani GV et al: Chronic heart failure: Contemporary diagnosis and management. Mayo Clin Proc 85:180, 2010.
5. McMurray JJ et al: PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 371:993, 2014.
6. Shah SJ et al: Phenotype-specific treatment of heart failure with pre- 1779 served ejection fraction: A multiorgan roadmap. Circulation 134:73, 2016.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:1810.
8. Braunwald E: Heart failure. JACC Heart Fail 1:1, 2013.
9. Braunwald E: The war against heart failure: The Lancet lecture. Lancet 385:812, 2015.
10. Gao J, Zhang X, Xu M, Deng S, Chen X. The efficacy and safety of sacubitril/valsartan compared with ACEI/ARB in the treatment of heart failure following acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2023 Aug 4;14:1237210. doi: 10.3389/fphar.2023.1237210. PMID: 37601056; PMCID: PMC10436296.

11. Jadhav U, Nair T, Mohanan P, et al. (September 14, 2023) Impact of Mineralocorticoid Receptor Antagonists in the Treatment of Heart Failure: Targeting the Heart Failure Cascade. Cureus 15(9): e45241. doi:10.7759/cureus.45241
12. Shivamadhu, Shivani MDa; Jalal, Aysha M. MDc; Sandhu, Arshbeer S. MDb; Persad, Narendra MDd; et al; Immunizing hearts: exploring the vaccination frontier in heart failure management ; Annals of Medicine & Surgery 86(1):p 300-307, January 2024. | DOI: 10.1097/MS9.0000000000001486
13. Alison Bailey, MD, FACC; Asgher Champsi, MB ChB; ESC Hot Line: DIG-META: Digoxin in Heart Failure and Atrial FibrillationOct 10, 2023 |
14. Ileana L. Piña,Carl S. Apstein,Gary J. Balady, Romualdo Belardinelli, Bernard R. Chaitman, et al, Heart Failure: Exercise and Activity A Statement From the American Heart Association Committee on Exercise, Rehabilitation, and Prevention; Originally published4 Mar 2003https://doi.org/10.1161/01.CIR.0000055013.92097.40Circulation. 2003;107:1210–1225
15. Colin-Ramirez E., McAlister F., Zheng Y., Sharma S., Ezekowitz J.A. Changes in dietary intake and nutritional status associated with a significant reduction in sodium intake in patients with heart failure. A sub-analysis of the SODIUM-HF pilot study. Clin. Nutr. ESPEN. 2016;11:e26–e32. doi: 10.1016/j.clnesp.2015.11.002.
16. Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch.,et al, for the VICTORIA Study Group*Author Info & Affiliations Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction, Published March 28, 2020 N Engl J Med 2020;382:1883-1893
17. Barrese V., Taglialatela M. New advances in beta-blocker therapy in heart failure. Front. Physiol. 2013;4:323. doi: 10.3389/fphys.2013.00323.
18. Ide T, Ohtani K, Higo T, Tanaka M, Kawasaki Y, Tsutsui H. Ivabradine for the Treatment of Cardiovascular Diseases. Circ J. 2019 Jan 25;83(2):252-260.

MANAGEMENT OF HYPERTENSION IN PRIMARY CARE

Albana Gjyzari[1], Ramadan Bara[1], Paola Jonuzi[1], Ilir Gjyzari[2], Migena Qato[1], Gentjan Asllanaj[1]
[1]University Hospital Center "Nënë Tereza", Tirana
[2]Health Center No. 7, Tirana
Correspondent E-mail: albana.gjyzari@umed.edu.al

Abstract

Introduction: Arterial hypertension is the most frequent chronic disease, which is observed in primary care. It is a serious problem, which has a great impact on the community, individuals and health care centers.

Methods: The aim of the study was to evaluate the clinical characteristics of hypertension and its treatment. The study included adult patients diagnosed with hypertension according to the Global Hypertension Practice Guidelines (2020) of the International Society of Hypertension and followed by the general practitioner in the primary health care service.

Results: A total of 70 patients participated in the study, of which 39 men (55.7%) and 31 women (42.3%), with an average age of 44.9 ±5.2 years. The most predisposed age group for men was 45-50 years old, while for women 50-55 years old. Forty-one percent of men with arterial hypertension were smokers. Obesity was found in 38% of male patients and about 42% of female patients. Ten percent of patients were treated with drug monotherapy, 70% with two drugs and 14.2% with triple therapy.

Conclusions: The burden of chronic diseases, including hypertension, is increasing globally, being associated with a large number of patients who require follow-up for long periods of time by health systems. Adequate management by coordinated medical teams can slow progression to damage of other organs, thereby reducing morbidity and mortality in these patients.

Keywords: Hypertension, primary health care.

MENAXHIMI I HIPERTENSIONIT NË KUJDESIN PRIMAR

Abstrakt

Hyrje: Hipertensioni arterial është një nga sëmundjet kronike më të shpeshta, që vërehet në shërbimin shëndetësor parësor. Është një problem serioz, i cili ka ndikime të rëndësishme në komunitet, individë dhe qendra shëndetësore.

Metoda: Qëllimi i studimit ishte vlerësimi i karakteristikave klinike të hipertensionit dhe trajtimit te tij. Ne studim janë përfshirë pacientë adult të diagnostikuar me hipertension sipas Udhëzimeve Globale të Praktikës së Hipertensionit (2020) të Shoqatës Ndërkombëtare të Hipertensionit dhe të ndjekur nga mjeku i përgjithshëm në shërbimin e kujdesit shëndetësor parësor.

Results: Në studim morën pjesë gjithsej 70 pacientë, nga të cilët 39 meshkuj (55.7%) dhe 31 femra (42.3%), me një moshë mesatare 44.9 ±5.2 vjeç. Grupmosha më e predispozuar për

meshkujt ishte 45-50 vjeç, ndërsa për femrat 50-55 vjeç. Dyzet e një përqind e meshkujve me hipertension arterial ishin duhanpirës. Obeziteti u gjet në 38% të pacientëve meshkuj dhe rreth 42% të pacienteve femra. Dhjetë përqind e pacientëve ishin në trajtim me monoterapi medikamentoze, 70% terapi me dy medikamente dhe 14.2% me triple terapi.
Konklusion: Barra e sëmundjeve kronike, mes tyre edhe e hipertensionit po rritet globalisht, duke u shoqëruar me numër të madh pacientësh, të cilët kërkojnë ndjekje për periudha të gjata kohore nga sistemet shëndetësore. Manaxhimi adekuat prej ekipeve mjekësore të koordinuara mund të ngadalësojë përparimin drejt dëmtimit të organeve të tjera, duke ulur kështu morbiditetin dhe mortalitetin në këta pacientë.

Fjalë kyçe: Hipertension, kujdes shëndetësor parësor.

Introduction

The prevalence of arterial hypertension (HTN) is estimated at 1 billion individuals worldwide. The World Health Organization reports that uncontrolled hypertension is responsible for 62% of cerebrovascular accidents (CVA) and 49% of ischemic heart disease (IHD), with little variation by gender. In addition, uncontrolled HTN is the leading risk factor for death worldwide, accounting for 19% (10.8 million) of all deaths (1, 2). Despite numerous clinical practice guidelines for the management of arterial hypertension, implementation remains insufficient with blood pressure control in less than 30% of cases even in high-income countries (3). According to the data of the Global Health Observatory, in all the regions of the World Health Organization (WHO), the prevalence of arterial hypertension was high in Albania, about 41% during the last decades (4). Primary health care teams play an important role in the management of hypertension through public awareness campaigns, assessment and investigation, diagnosis and treatment of hypertension cases to achieve good control and prevent potential complications.

Arterial hypertension is a major risk factor for cardiovascular diseases. The prevalence of the disease has been increasing both globally and nationally as a result of socioeconomic development and urbanization, unhealthy diet, tobacco and alcohol use, and sedentary lifestyles.

1. Systemic arterial hypertension refers to a sustained systemic increase in arterial blood pressure (BP). It is defined as a resting systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg (5, 6).
A. Essential hypertension (primary hypertension): contributes to about 95% of cases of hypertension. The main causes in these patients are genetic and environmental factors (5, 6).
B. Secondary hypertension: contributes to about 5% of cases of hypertension in which the cause of high blood pressure can be identified (5, 6).
2. Isolated systolic hypertension: high SBP values (≥ 140 mmHg) and normal DBP values (<90 mmHg) (5, 6).
3. White coat hypertension: is a BP measured in the office and is usually higher than the BP measured outside the office in untreated persons. This is attributed to the stress response, anxiety and/or conditioned response to the unusual situation (5, 6).
4. Masked hypertension: BP that is normal in the office and abnormally high outside the medical setting in untreated persons, also called isolated ambulatory hypertension (5, 6).

5. Orthostatic hypotension: defined as a reduction in PAS of >20 mmHg or PAD of >10 mmHg within 3 minutes from supine to standing (5, 6).
6. Resistant hypertension: when a medication regimen that includes appropriate lifestyle modification measures plus a diuretic (if not contraindicated) and two other antihypertensive medications in full or maximally tolerated doses fails to lower blood pressure to values optimal (5, 6).
7. Refractory hypertension: includes those patients with resistant hypertension who cannot keep BP under control, even with maximum therapy (four or more medications with complementary mechanisms given in maximum tolerated doses) under the care of a hypertension specialist (5, 6).

Table 1. Classification of arterial hypertension based on office blood pressure (BP) measurement (7).

Stages	Systolic (mm Hg)		Diastolic (mm Hg)
BP Normal	<130	and	<85
BP raised within normal limits	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	≥160	and/or	≥100

Material and method

This cross-sectional study included patients from a primary care clinic in Tirana during the period April - May 2022. The study included 70 patients aged ≥40 years with previously diagnosed hypertension PAS ≥140 mmHg and or PAD ≥90 mmHg.
Patients with active systemic disease (fever) and pregnant women were excluded.

The aim of the study was to evaluate the demographic, clinical and laboratory indicators in patients diagnosed with arterial hypertension. Adult patients diagnosed with hypertension according to the Global Hypertension Practice Guidelines (2020) of the International Society of Hypertension (ISH) and followed by a general practitioner in a primary health care service were included in the study. BP measurement was carried out according to the recommendations given by the guidelines (7). The included laboratory examinations were lipid profile (total cholesterol and its fractions, HDL and LDL cholesterol, triglycerides), and glycemic profile (fasting and 2-hour postprandial glycemia and HbA1c).

Information was collected on sociodemographic data, comorbidities, diet, lifestyle and tobacco use.

Consent was obtained from individuals included in the study and they also completed questionnaires regarding smoking, physical activity, knowledge about diet and hypertension management.

Statistical analysis:

For data analysis was used SPSS program ver. 15.00. For continuous variables, values are presented as mean and standard deviation (M±SD). For categorical variables, percentage distributions were reported. The differences were called significant for the two-sided value of $p<0.05$.

Results

Table 2. Prevalence of hypertension according to age group and gender

Age group (years)	Male n (%)	Female n (%)	Total n (%)
40-49	13 (18.5)	8 (11.4)	21 (30)
50-59	7 (10)	11 (15.7)	18 (25.7)
60-69	8 (11.4)	4 (5.7)	12 (17.1)
≥70	11 (15.7)	8 (11.4)	19 (27.1)
Total	39 (55.7%)	31 (44.3%)	70 (100%)

A total of 70 patients participated in the study, of which 39 men (55.7%) and 31 women (44.3%), with an average age of 44.9 ±5.2 years. The most predisposed age group for men was 40-49 years old, while for women 50-59 years old.

Table 3. Risk factors for arterial hypertension according to gender

	Male 39 (55.7%)	Female 31 (44.3%)
Smoker n (%)	16 (41)	0
Overweight/Obesity n (%)	15 (38)	13 (42)
Rural area n (%)	12 (31)	8 (25)
Alcohol n (%)	4 (10)	0
Physical activity n (%)	18 (47)	10 (32)

From the data obtained after the questionnaire survey, it was found that hypertension in men is related to the status of a smoker, where 41% of men with arterial hypertension were smokers. Hypertension levels were higher among overweight/obese interviewees compared to those of normal weight, where about 38% of men and about 42% of women had BMI values >25. About 47% of men and 32% of women performed physical activity.

Table 4. Arterial pressure measured in the office in patients with hypertension under medication

Systolic BP	N (%)	Diastolic BP	N (%)
<130 mmHg	7 (10)	<85 mmHg	8 (11.4)
130–139 mmHg	27 (38.6)	85–89 mmHg	28 (40)
140–159 mmHg	28 (40)	90–99 mmHg	32 (45.8)
≥160 mmHg	8 (11.4)	>110 mmHg	2 (2.8)

From the data, it is noted that about 50% of patients diagnosed with arterial hypertension did not have their blood pressure under optimal control.

Table 5. Lipid profile in patients with HTA under medication

Dyslipidemia	N (%)	Value M ±SD
Total cholesterol >220 mg/dl	25 (35.7)	224.2 ±50.1
Triglyceride>150 mg/dl	20 (28.5)	125.4 ±71.3
HDL <35 mg/dl	26 (37)	30.1±10.2
LDL>100 mg/dl	24 (34.2)	161.5 ±23.1

Total cholesterol was found to be elevated in 35.7% of hypertensive patients with an average value of 224.2 mg/dl, in 28.5% of cases triglycerides were found to be elevated with an average value of 125.4 mg/dl and in 34.2% of cases the values of LDL were high, with a mean value of 161.5 mg/dl. Regarding HDL, about 37% of patients had low values, which is directly related to the risk of cardiovascular events.

Table 6. Prevalence of concomitant diseases

Diseases	N (%)
Diabetes Mellitus	8 (11.4)
Chronic renal disease	9 (12.8)
Cardiac disease	25 (35.7)

11.4% of patients with hypertension had also Diabetes Mellitus with HbA1c values from 7.5-13.8%.

Table 7. Non-pharmacological management of arterial hypertension

	Cases (n)	%
Diet	60	85%
Physical activity	28	40%
Alcohol/ smoke cessation	20	28.5%

Almost half of men 47%, and nearly a third of women 32%, were trying to control weight or lose weight through physical activity and a healthy diet, while 85% of patients reported trying to control salt intake in their diet.

Table 8. Drug management of arterial hypertension

	Cases (n)	%
ACE-inhibitors/ARB	59	84.5%
Ca-blockers	48	68.5%
Diuretic	24	34.2%
Other medications*	14	20%
Monotherapy	7	10%
Dual therapy	49	70%
Triple therapy	10	14.2%

*Amiloride, doxazosin, methyldopa, moxonidin, eplerenone, beta-blockers
About 46 (65.7%) of the patients were compliant with medication therapy for the treatment of arterial hypertension, 24(61%) males and 22(71%) females.

Discussion

Comprehensive study analyzes have shown that since 1990 the prevalence of hypertension worldwide has increased and the number of people with hypertension has doubled, with most of the increase occurring in low- and middle-income regions. In high-income countries, prevalence has declined, and about 80% of patients with HTN are under treatment, with good BP control in up to 60% (8).
In accordance with most major guidelines, it is recommended that hypertension be diagnosed when the clinical SBP is ≥140 mm Hg and/or the DBP ≥90 mm Hg on several consecutive examinations. Elevated BP within normal limits aims to identify individuals who may benefit from lifestyle interventions and those who are recommended to start pharmacological treatment if indications are present according to the clinical situation. 2-3 office visits at 1–4-week intervals (depending on blood pressure level) are necessary to confirm the diagnosis of hypertension. Diagnosis can be made in a single visit, if BP is ≥180/110 mmHg and there is evidence of cardiovascular disease (CVD) (5).
From the data of our study, hypertension was more prevalent in men (55.7%). This difference in the prevalence of HTN between the genders is attributed to differences in the type of diet, lifestyle choices, level of physical activity, and some genetic variation (9). The highest prevalence of hypertension in men was at the age of 40-49 years, and in women at the age of 50-59 years. A high prevalence of hypertension was observed in the age over 70 years for both men and women. Isolated systolic hypertension SBP (≥140 mm Hg) and low DBP (<90 mm Hg) is common in the elderly, in whom it reflects stiffening of the large arteries with an increase in pulse pressure (difference between SBP and DBP). Although hypertension is not directly related to the female gender, aspects such as: pregnancy, pregnancy planning and menopause can increase the risk of its development. The likelihood of developing hypertension increases significantly during menopause in women.
Gender, age, race and heredity are risk factors for HTA, which cannot be modified, but lifestyle such as obesity, diet, physical inactivity, stress, use of certain medications, smoking, excessive alcohol consumption are modifiable risk factors.
As mentioned in earlier studies (10), in our study we found also a high prevalence of risk factors such as smoking (41% of men), overweight/obesity (38% of men, and about 42% of women), excessive alcohol consumption (10% of men), physical inactivity (53% of men, 68% of women). More than 50% of patients with hypertension have cardiovascular risk factors (11). The most common risk factors are diabetes (15%-20%), dyslipidemia (elevated LDL-C and triglycerides [30%]), overweight-obesity (40%), hyperuricemia (25 %) and metabolic syndrome (40%), as well as unhealthy lifestyle (smoking, high alcohol consumption, sedentary lifestyle). Fasting blood glucose levels should be reduced below 126 mg/dL (7 mmol/L) and HbA1c below 7% (53 mmol/mol) (5). Treatment should include a statin if LDL >70 mg/dL (1.8 mmol/L) (diabetes with target organ damage) or >100 mg/dL (2.6 mmol/L) (uncomplicated diabetes). The presence of one or more cardiovascular risk factors increases the risk of coronary, cerebrovascular and renal diseases in hypertensive patients (5).

Hypertensive patients have several common comorbidities that may influence increased cardiovascular risk and treatment strategy. The number of concomitant diseases increases with age, with the prevalence of hypertension and other diseases. The most common comorbidities include coronary artery disease (CAD), cerebrovascular disease, chronic kidney disease (CKD), heart failure (HF).

In our study, about 35.7% of patients with HTN also had data on cardiac disease, which correspond to those in the literature (12). Lifestyle changes (smoking cessation, diet and exercise) are recommended. BP should be decreased if ≥140/90 mmHg and treated to achieve a target of <130/80 mmHg (<140/80 in elderly patients). Blockers of the renin angiotensin system (SRA), beta-blockers regardless of PA levels with or without calcium channel blockers are first-line medications in patients with hypertension (5). Lipid-lowering treatment with an LDL-C target of <55 mg/dL (1.4 mmol/L) (13) is very important. An antiplatelet agent (acetylsalicylic acid) is also recommended (5).

Hypertension is a major risk factor for the development and progression of albuminuria and any form of CVD (14). A lower glomerular filtration rate is associated with resistant hypertension, and high blood pressure values at night (14). Glomerular filtration, microalbuminuria and blood electrolytes should be monitored (5).

Treatment of hypertension

Choosing a healthy lifestyle can prevent or delay the onset of hypertension and can reduce cardiovascular risk (15). Lifestyle modification is also the first line of antihypertensive treatment. Lifestyle changes can also enhance the effects of antihypertensive treatment. It is recommended to reduce the amount of salt during food preparation and at the table, as well as avoiding the consumption of foods with a lot of salt such as fast foods and processed foods. Eating a diet rich in whole grains, fruits, vegetables, unsaturated fats and dairy products and reducing foods high in sugar, saturated fats (16). Adding vegetables to the diet that are high in nitrates known to reduce blood pressure, such as leafy greens and beets. Body weight control is necessary to avoid obesity. Abdominal obesity in particular needs to be managed. Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension (17). About 85% of our patients were trying to adjust their diet, and 40% were doing physical activity according to the doctor's advice.

Non-adherence to antihypertensive treatment is observed in 10%–80% of hypertensive patients and is one of the main factors of poor BP control (18). The etiology of nonadherence to antihypertensive treatment is multifactorial and includes causes related to the health care system, pharmacological therapy, disease, patients, and their socioeconomic status (19).

Conclusions

A multidisciplinary approach of the health care team is needed to improve the monitoring, follow-up and treatment of patients with arterial hypertension. It is recommended to reduce polypharmacy, e.g., the use of combinations in a single pill, as well as once-daily doses. Monitoring PA at home as well as empowering self-management counseling. In addition to BP control, the therapeutic strategy should include lifestyle changes, body weight control, and effective treatment of other risk factors in order to reduce cardiovascular risk.

References

1. Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. et al, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, & National High Blood Pressure Education Program Coordinating Committee (2003). Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension (Dallas, Tex. : 1979), 42(6), 1206–1252. https://doi.org/10.1161/01.HYP.0000107251.49515.c2
2. Global Burden of Disease Study 2019. Lancet. 2020
3. NCD Risk Factor Collaboration (NCD-RisC) (2019). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet (London, England), 394(10199), 639–651. https://doi.org/10.1016/S0140-6736(19)31145-6
4. World Health Organization. Raised Blood Pressure. https://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/
5. Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., et al, Authors/Task Force Members: (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Journal of hypertension, 36(10), 1953–2041. https://doi.org/10.1097/HJH.0000000000001940
6. Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Jr, Collins, K. J., Dennison Himmelfarb, et al,(2018). 2017 ACC/AHA/AAPA/ABC/ ACPM/AGS/APhA/ ASH/ASPC/ NMA/ PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension (Dallas, Tex. : 1979), 71(6), 1269–1324.
7. Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, et al, (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension (Dallas, Tex. : 1979), 75(6), 1334–1357.
8. NCD Risk Factor Collaboration (NCD-RisC) (2021). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet (London, England), 398(10304), 957–980. https://doi.org/10.1016/S0140-6736(21)01330-1
9. Ruixing, Y., Jinzhen, W., Shangling, P., Weixiong, L., Dezhai, Y., & Yuming, C. (2008). Sex differences in environmental and genetic factors for hypertension. The American journal of medicine, 121(9), 811–819. https://doi.org/10.1016/j.amjmed.2008.04.026
10. Kannel W. B. (1989). Risk factors in hypertension. Journal of cardiovascular pharmacology, 13 Suppl 1, S4–S10. https://doi.org/10.1097/00005344-198900131-00003

11. Lopez, A. D., Mathers, C. D., Ezzati, M., Jamison, D. T., & Murray, C. J. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet (London, England), 367(9524), 1747–1757. https://doi.org/10.1016/S0140-6736(06)68770-9
12. Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, et al, L., & INTERHEART Study Investigators (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet (London, England), 364(9438), 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9
13. Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, et al, ESC Scientific Document Group (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European heart journal, 41(1), 111–188. https://doi.org/10.1093/eurheartj/ehz455
14. Drawz, P. E., Alper, A. B., Anderson, A. H., Brecklin, C. S., Charleston, J., Chen, J., et al, Chronic Renal Insufficiency Cohort Study Investigators (2016). Masked Hypertension and Elevated Nighttime Blood Pressure in CKD: Prevalence and Association with Target Organ Damage. Clinical journal of the American Society of Nephrology : CJASN, 11(4), 642–652. https://doi.org/10.2215/CJN.08530815
15. Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, et al, ESC Scientific Document Group (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal, 37(29), 2315–2381. https://doi.org/10.1093/eurheartj/ehw106
16. Gay, H. C., Rao, S. G., Vaccarino, V., & Ali, M. K. (2016). Effects of Different Dietary Interventions on Blood Pressure: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hypertension (Dallas, Tex. : 1979), 67(4), 733–739. https://doi.org/10.1161/HYPERTENSIONAHA.115.06853
17. Cornelissen, V. A., & Smart, N. A. (2013). Exercise training for blood pressure: a systematic review and meta-analysis. Journal of the American Heart Association, 2(1), e004473. https://doi.org/10.1161/JAHA.112.004473
18. Corrao, G., Parodi, A., Nicotra, F., Zambon, A., Merlino, L., Cesana, G., & Mancia, G. (2011). Better compliance to antihypertensive medications reduces cardiovascular risk. Journal of hypertension, 29(3), 610–618. https://doi.org/10.1097/HJH.0b013e328342ca97
19. Chaudri N. A. (2004). Adherence to Long-term Therapies Evidence for Action. Annals of Saudi Medicine, 24(3), 221–222. https://doi.org/10.5144/0256-4947.2004.221

UNRAVELING THE GUARDIAN OF THE GENOME: THE ROLE OF P53 IN CHRONIC LYMPHOCYTIC LEUKEMIA

Elsuarta Calliku, Alma Cili, Adela Perolla, Tatjana Caja, Polikron Pulluqi, Arben Ivanaj.
Hematology, UHC "Mother Tereza"

Correspondent E-mail: elacalliku@gmail.com

Abstract

Chronic Lymphocytic Leukemia is a prevalent form of adult leukemia characterized by a heterogeneous clinical course and variable responses to therapy. The p53 protein, often dubbed "the guardian of the genome," plays a pivotal role in cellular responses to DNA damage, including cell cycle arrest, DNA repair, and apoptosis. Mutations in the TP53 gene, which encodes the p53 protein, or alterations in the p53 pathway, are of particular interest in Chronic Lymphocytic Leukemia due to their association with treatment resistance, aggressive disease progression, and poor prognosis. This article synthesizes recent research on the role of p53 in Chronic Lymphocytic Leukemia, emphasizing its impact on disease biology, therapeutic resistance, and clinical outcomes. Studies reveal that p53 mutations not only contribute to chemotherapy resistance but also delineate a subset of patients with significantly worse prognoses. The aberrant expression of p53-regulated non-coding RNAs and alterations in p53 signaling pathways further illustrate the complex role of p53 in Chronic Lymphocytic Leukemia pathogenesis and response to treatment. Furthermore, the interaction between p53 and other cellular pathways, such as Notch signaling, presents new opportunities for targeted therapeutic strategies. These insights underscore the critical role of p53 in Chronic Lymphocytic Leukemia and highlight the need for novel approaches to overcome p53-mediated resistance mechanisms, offering a beacon of hope for improving patient outcomes in this challenging disease.

Keywords: Chronic Lymphocytic Leukemia, p53 pathway, TP53 mutations, Targeted therapies

ZBËRTHIMI I MBROJTESIT TË GJENOMIT: ROLI I P53 NË LEUCEMINË KRONIKE LIMFATIKE

Abstrakt

Leucemia limfocite kronike është një formë mbizotëruese e leucemisë së moshës së rritur që karakterizohet nga një dekurs klinik heterogjen dhe përgjigje të ndryshme ndaj terapisë. Proteina p53, shpesh e quajtur «gardiani i gjenomit», luan një rol thelbësor në përgjigjet qelizore ndaj dëmtimit të ADN-së, duke përfshirë ndalimin e ciklit qelizor, riparimin e ADN-së dhe apoptozën. Mutacionet në gjenin TP53, i cili kodon proteinën p53, ose ndryshimet në shtegun p53, janë me interes të veçantë në Leuceminë limfoide kronike për shkak të shoqërimit të tyre me rezistencën ndaj trajtimit, përparimin agresiv të sëmundjeve dhe prognozën e erret. Ky artikull sintetizon kërkimet e fundit mbi rolin e p53 në Leuceminë limfoide kronike duke theksuar ndikimin e tij në biologjinë e sëmundjes, rezistencën terapeutike dhe rezultatet klinike. Studimet zbulojnë se mutacionet p53 jo vetëm që kontribuojnë në rezistencën ndaj kimioterapisë,

por edhe përcaktojnë një nën-grup pacientësh me prognoze dukshëm më të keqe. Shprehja aberrante e RNA-ve jo koduese të rregulluara nga P53 dhe ndryshimet në rrugët e sinjalizimit p53 ilustrojnë më tej rolin kompleks të p53 në patogjenezën e Leucemisë limfoide kronike dhe reagimin ndaj trajtimit. Për më tepër, ndërveprimi midis p53 dhe rrugëve të tjera qelizore, si sinjalizimi Notch, paraqet mundësi të reja për strategji terapeutike të synuara. Këto njohuri theksojnë rolin kritik të p53 në Leuceminë limfoide kronike dhe theksojnë nevojën për qasje të reja për të kapërcyer mekanizmat e rezistencës të ndërmjetësuara nga P53, duke ofruar një dritë shprese për përmirësimin e rezultateve të pacientëve në këtë sëmundje sfiduese.

Fjalë kyçe: Leucemia kronike limfatike , shtegu p53, mutacionet TP53, terapitë target.

Introduction

Chronic Lymphocytic Leukemia (CLL) presents a significant challenge in hematologic malignancies due to its heterogeneity and variable prognosis. Central to the pathogenesis and progression of CLL is the tumor suppressor protein p53, dubbed "the guardian of the genome" for its pivotal role in maintaining genomic stability. p53 exerts its effects through various mechanisms, including the induction of apoptosis, cell cycle arrest, and DNA repair, in response to cellular stress. Mutations or dysregulation of the p53 pathway are associated with aggressive disease phenotypes, resistance to conventional chemotherapy, and poor clinical outcomes in CLL patients. This article provides an overview of recent research findings on the role of p53 in CLL, emphasizing its significance in disease pathology, therapeutic resistance, and implications for treatment strategies.

The impact of p53 mutations on chemotherapy resistance and prognosis in CLL has been well-documented. Blume et al. (2015) highlighted the importance of understanding non-coding RNA targets of p53 in CLL, revealing a landscape of p53-dependent microRNA/non-coding RNA induced in response to DNA damage (1) Similarly, Işın et al. in 2012 demonstrated a significant association between the expression of p53, p14ARF, and HDM2 genes and CLL, suggesting their involvement in the disease's pathophysiology (2). Alterations in the expression and function of p53 isoforms further complicate the disease's behavior. Sellmann et al. (2012) found a strong correlation between deletions of 17p13, accumulation of full-length p53 protein, and adverse outcomes in CLL, indicating the contribution of p53 isoforms to CLL pathogenesis (3) The complexity of the p53 pathway in CLL is further illustrated by Wickremasinghe et al. (2011), who discussed the interplay between p53 and the Notch signaling pathway in controlling apoptosis in CLL cells, proposing novel therapeutic strategies based on this interaction (4)

Recent studies have also explored the genetic interplay affecting the p53 pathway in CLL. Jalilian et al. (2021) investigated p53 and MDM2 polymorphisms in CLL patients, suggesting a complex genetic interaction that may influence disease susceptibility and progression (5).

The critical role of p53 in CLL underscores the necessity for innovative therapeutic approaches targeting the p53 pathway. Understanding the multifaceted role of p53 in CLL not only provides insights into the disease's molecular underpinnings but also opens avenues for the development of targeted therapies aimed at overcoming resistance mechanisms and improving patient outcomes.

Understanding P53:

P53, colloquially termed the "genome's sentinel," occupies a pivotal position in the cellular defense against malignancy, orchestrating an elaborate suite of responses such as cell cycle cessation, programmed cell death, DNA rectification, and cellular aging processes. Its cardinal role in regulating a broad spectrum of cellular functions not only accentuates its intricacy but also underscores its significance in oncological research, including its implications for Chronic Lymphocytic Leukemia (CLL). Ongoing investigations have progressively unveiled the diverse roles of p53, shedding light on its influence over tumor suppression, metabolic control, redox regulation, and more. This exploration into p53's multifaceted network and its aberrations opens promising vistas for therapeutic interventions in cancer.

In the recent discourse, Boutelle and Attardi (2021) delineate the extensive network governed by p53, pointing out its transcriptional targets across various cellular mechanisms vital for thwarting oncogenesis. Likewise, Bernard E et al. (2020) probe into the interplay between p53 and the Apoptosis Inhibitor Proteins (IAPs) within colorectal cancer, delineating the therapeutic promise of targeting their interplay for cancer mitigation.

Further contributing to the nuanced understanding of p53's transcriptional landscape, Olivero et al. (2020) elucidate the significance of Pvt1b, a p53-responsive isoform of the long noncoding RNA Pvt1, in downregulating Myc transcription and counteracting cancer development. Concurrently, Liu et al. (2020) investigate the symbiosis between p53 and the TRIM protein family, highlighting the complex regulatory schema of p53 facilitated by post-translational modifications.

Moreover, the role of p53 in modulating ferroptosis—an iron-dependent form of cell death marked by lipid peroxidation—emerges as a salient aspect of its tumor-suppressive functionality. Liu et al. (2020) provide a comprehensive review of how p53 and its pathways regulate ferroptosis, suggesting innovative therapeutic strategies for cancer and other diseases.

As the body of research advances, the intricate network presided over by p53 continues to be a focal point for unraveling the molecular underpinnings of cancer and spearheading the development of targeted therapeutic modalities. The regulatory complexity and multifunctionality of p53 offer both challenges and opportunities for harnessing its potential in the fight against cancer.

The tumor suppressor protein p53, renowned as the "guardian of the genome," plays a seminal role in the cellular defense against carcinogenesis by modulating cell cycle progression, apoptosis, DNA repair, and cellular senescence. Its deregulation or mutation notably contributes to the pathogenesis of Chronic Lymphocytic Leukemia (CLL), a disease characterized by the aberrant accumulation of functionally incompetent lymphocytes. Research over the past years has increasingly highlighted the multifactorial nature of CLL, involving genetic mutations, epigenetic alterations, and disruptions in cellular signaling pathways, with alterations in the p53 pathway being of particular significance due to their profound impact on disease progression and response to treatment.

Mutations in the TP53 gene, encoding the p53 protein, or alterations affecting components of the p53 pathway can critically impair cellular mechanisms responsible for genomic stability and the DNA damage response. Such aberrations are linked to aggressive disease manifestations, chemotherapy resistance, and poorer prognostic outcomes in CLL. The loss of functional p53 facilitates the relentless proliferation of malignant cells and contributes to the genetic instability

that underlies CLL progression. Furthermore, the significance of p53 extends beyond tumor suppression. It intersects with various cellular pathways, influencing apoptosis, metabolism, and immune responses to neoplastic cells. The interaction between p53 and regulators of apoptosis, for instance, is pivotal for the clearance of cells harboring potentially oncogenic mutations. Disruption of this interaction in CLL not only enables the survival of malignant cells but also supports their evasion from immune surveillance. Recent investigations have also underscored the importance of p53 in determining the therapeutic responsiveness in CLL. DNA-damaging agents, which form the backbone of CLL therapy, rely on an intact p53 pathway to exert their cytotoxic effects. Consequently, CLL patients harboring defective p53 signaling frequently exhibit resistances to a broad spectrum of chemotherapeutic agents, underscoring the urgent need for novel therapeutic strategies that can either bypass or restore p53 functionality.

Several studies have significantly contributed to our understanding of p53's role in CLL:

a. Blume et al. (2015) mapped out the landscape of p53-dependent microRNA/non-coding RNA induced in response to DNA damage in CLL, identifying key targets such as miR-34a, NEAT1, and lincRNA-p21, which are essential components of the p53-dependent DNA damage response machinery in CLL (1).
b. Abdullah et al. (2015) investigated the correlation between p53 protein expression and various clinicopathological factors in CLL, highlighting the significance of p53 as a prognostic marker in the disease's progression (10).
c. Jalilian et al. (2021) explored the impact of p53 and MDM2 polymorphisms on CLL pathogenesis, suggesting the interaction between these genotypes may confer susceptibility to CLL, and highlighting the complexity of the p53 pathway in CLL (5).

P53's role in CLL pathogenesis is intricate, influencing disease behavior, therapeutic response, and patient prognosis. Understanding the mechanisms underlying p53 dysfunction in CLL is crucial for developing targeted therapies and improving patient outcomes. As research continues to unravel the complexities of the p53 pathway, it holds the promise of opening new avenues for the treatment and management of CLL.

Impact on Treatment Response:

The influence of p53 dysfunction on treatment response in Chronic Lymphocytic Leukemia (CLL) is a critical area of study, given p53's role in regulating cell cycle progression, apoptosis, DNA repair, and cellular senescence. Aberrations within the p53 pathway, particularly mutations in the TP53 gene or alterations affecting its functionality, substantially impact the effectiveness of therapies designed to treat CLL, leading to chemoresistance and poorer prognostic outcomes.

a) Chemotherapy Resistance

Mutations or dysregulation of the p53 pathway confer resistance against various chemotherapeutic agents, primarily through the impaired apoptotic response of cells to DNA damage. Blume et al. (2015) highlighted the complexity of p53-dependent non-coding RNA networks in CLL, illustrating how mutations in the TP53 gene lead to chemotherapy resistance and a grim prognosis (1).

b) Targeted Therapies and Novel Agents

The advent of targeted therapies such as ibrutinib, a Bruton's tyrosine kinase inhibitor, and venetoclax, a BCL-2 inhibitor, has offered new hope. Moia and colleagues (2020) discussed the potential therapeutic options for TP53-disrupted patients, emphasizing agents that circumvent TP53 disruption, restore the function of mutant p53, or potentiate p53 function (11).

c) Restorative Approaches

Emerging strategies aim to restore p53 function or modulate the pathway to trigger tumor cell death. Molica et al. (2023) explored multiple therapeutic approaches to tackle TP53 dysfunction in high-risk CLL, suggesting the use of inhibitors and small-molecule p53 reactivators to improve outcomes (12).

d) Clinical Trials and Future Directions

Clinical trials have been instrumental in evaluating the efficacy of compounds targeting p53 dysfunction. For instance, O'Brien et al. (2016) conducted a study on ibrutinib for patients with relapsed or refractory CLL with 17p deletion, highlighting the drug's potential despite the challenges posed by p53 pathway aberrations (13).

And while the advent of targeted therapies has improved treatment options for CLL patients with p53 dysfunction, the search for more effective treatments continues. The development of novel therapeutic strategies that can overcome or bypass p53-mediated resistance mechanisms remains a priority, aiming to improve outcomes for this challenging subgroup of CLL patients.

Therapeutic Targeting of P53:

The pursuit of therapeutic strategies aimed at the p53 pathway in Chronic Lymphocytic Leukemia (CLL) constitutes a crucial area of exploration, especially for individuals bearing TP53 genetic aberrations, who typically exhibit suboptimal responses to conventional treatment modalities. Given the central role of p53 in orchestrating cellular responses to genotoxic stress, including apoptosis, DNA repair, and cell cycle regulation, and its frequent inactivation across a broad spectrum of malignancies, strategies to reactivate or simulate its tumor-suppressive functions are under intensive investigation.

a) Reinstating P53 Activity

Approaches focused on directly reinstating the activity of mutated p53 proteins or modulating the p53 pathway to trigger apoptosis in tumor cells are gaining traction. Compounds such as PRIMA-1MET, designed to reactivate mutant forms of p53, have shown promise in preclinical studies and CLL patient samples, suggesting a capability to counteract therapeutic resistance and initiate apoptotic processes in CLL cells harboring TP53 mutations (14,15). Furthermore, the exploration of agents like Protoporphyrin IX that inhibit both p53/MDM2 and p53/MDM4 interactions reveals a potential mechanism for inducing apoptosis in B-cell CLL without harming normal cells (16).

b) Disrupting MDM2-P53 Interactions

Targeting the interaction between MDM2 and p53 has emerged as a pivotal strategy for therapeutic intervention, aiming to disrupt this interaction and thus prevent MDM2-mediated p53 degradation. Clinical developments include MDM2 antagonists like idasanutlin, which specifically target the MDM2-p53 interface, potentially reinstating the tumor-suppressive functions of p53 in various cancers, including CLL (17).

c) Clinical Trials and Targeted Therapy

The clinical efficacy of ibrutinib, a Bruton's tyrosine kinase inhibitor, even in patients with TP53 deletions, underscores the utility of targeted therapies that, while not directly modulating p53, offer significant anti-tumor effects by engaging other pathways. The findings from the RESONATE-17 trial illustrate ibrutinib's role in enhancing the prognosis for CLL patients with TP53 mutations, offering an effective treatment pathway for this subgroup (13).

d) Innovative Strategies and Future Directions

Innovative therapeutic approaches continue to be developed, including those that leverage the activation of TAp73, a relative of p53, to bypass drug resistance in cases of p53 dysfunction, thereby inducing cell death through alternative apoptotic pathways (18).

Exploring therapeutic avenues targeting the p53 pathway in CLL is an evolving and promising field. Through direct activation of p53's tumor-suppressive functions, disruption of p53-inhibiting interactions, or the use of targeted therapies that obviate the need for p53, new strategies are broadening the treatment landscape for CLL. This ongoing innovation in therapeutic development underscores the shift towards precision medicine in addressing the complexities of CLL, particularly for patients with deficiencies in the p53 pathway.

Conclusions

In summary, the treatment paradigm for Chronic Lymphocytic Leukemia (CLL) is witnessing a pivotal shift, underscored by breakthroughs in the comprehension and targeting of the p53 signaling pathway. The paramount importance of p53 in maintaining cellular equilibrium and its tumor-suppressive capabilities highlights its strategic significance in therapeutic development, particularly for those afflicted with CLL and bearing TP53 genetic aberrations, who traditionally have poor prognoses. Initiatives focused on reviving p53's dormant functions, impeding its detrimental interactions, or leveraging targeted therapeutics that circumvent the necessity of p53 functionality, are opening new pathways to surmount therapeutic resistance and enhance patient care outcomes.

The progression within this domain, marked by the initiation of clinical trials evaluating MDM2 inhibitors and pioneering compounds designed to rehabilitate or amplify p53 activity, signifies a considerable leap forward. These advancements not only kindle optimism among patients with deficiencies in the p53 pathway but also highlight a transition towards tailored, precision-medicine strategies in the management of CLL. As ongoing research continues to unravel the intricate dynamics of the p53 pathway and its myriad interactions, the prospects for inventive therapeutic approaches to augment patient well-being and survival prospects grow increasingly tangible. This evolution toward fully leveraging the therapeutic promise of targeting the p53 pathway in CLL is a testament to the relentless quest for novel cancer treatment modalities, each discovery laying the groundwork for future breakthroughs.

References

1. Blume, C., Hotz-Wagenblatt, A., Hüllein, J., Sellner, L., Sellner, L., Jethwa, et al,. (2015). p53-dependent non-coding RNA networks in chronic lymphocytic leukemia. Leukemia, 29, 2015-2023. https://doi.org/10.1038/leu.2015.119.
2. Isin, M., Yenerel, M., Aktan, M., Buyru, N., & Dalay, N. (2012). Analysis of p53 tumor suppressor pathway genes in chronic lymphocytic leukemia. DNA and cell biology, 31(5), 777–782. https://doi.org/10.1089/dna.2011.1314
3. Sellmann, L., Carpinteiro, A., Nückel, H., Scholtysik, R., Siemer, D., Klein-Hipass, et al, (2012). p53 protein expression in chronic lymphocytic leukemia. Leukemia & Lymphoma, 53, 1282 - 1288. https://doi.org/10.3109/10428194.2011.654115.

4. Wickremasinghe, R., Prentice, A., & Steele, A. (2011). p53 and Notch signaling in chronic lymphocytic leukemia: clues to identifying novel therapeutic strategies. Leukemia, 25, 1400-1407. https://doi.org/10.1038/leu.2011.103.
5. Jalilian, N., Maleki, Y., Shakiba, E., Aznab, M., Rahimi, Z., Salimi, M., & Rhimi, Z. (2021). p53 p.Pro72Arg (rs1042522) and Mouse Double Minute 2 (MDM2) Single-Nucleotide Polymorphism (SNP) 309 Variants and Their Interaction in Chronic Lymphocytic Leukemia (CLL): A Survey in CLL Patients from Western Iran. International Journal of Hematology-Oncology and Stem Cell Research, 15, 160 - 169. https://doi.org/10.18502/ijhoscr.v15i3.6846.
6. Boutelle, A., & Attardi, L. (2021). p53 and Tumor Suppression: It Takes a Network.. Trends in cell biology. https://doi.org/10.1016/j.tcb.2020.12.011.
7. Bernard, E., Nannya, Y., Hasserjian, R. P., Devlin, S. M., Tuechler, H., Medina-Martinez, et al, (2020). Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nature medicine, 26(10), 1549–1556. https://doi.org/10.1038/s41591-020-1008-z.
8. Olivero, C., Martínez-Terroba, E., Zimmer, J., Liao, C., Tesfaye, E., Hooshdaran, et al, (2020). p53 Activates the Long Noncoding RNA Pvt1b to Inhibit Myc and Suppress Tumorigenesis.. Molecular cell. https://doi.org/10.2139/ssrn.3353218.
9. Liu, J., Zhang, C., Wang, X., Hu, W., & Feng, Z. (2020). Tumor suppressor p53 cross-talks with TRIM family proteins. Genes & Diseases, 8, 463 - 474. https://doi.org/10.1016/j.gendis.2020.07.003.
10. Abdullah, A., Jaafar, A., & Alsaadawi, A. (2015). Immunohistochemical study of p-53 protein expression in chronic lymphocytic leukemia and its correlation with clinicopathological factors. Journal of the Faculty of Medicine Baghdad. https://doi.org/10.32007/MED.1936/JFACMEDBAGDAD.V57I1.15.
11. Moia, R., Boggione, P., Mahmoud, A., Kodipad, A., Adhinaveni, R., Sagiraju, S., et al, (2020). Targeting p53 in chronic lymphocytic leukemia. Expert Opinion on Therapeutic Targets, 24, 1239 - 1250. https://doi.org/10.1080/14728222.2020.1832465.
12. Molica, S., Tam, C., Allsup, D., & Polliack, A. (2023). Targeting TP53 disruption in chronic lymphocytic leukemia: Current strategies and future directions.. Hematological oncology. https://doi.org/10.1002/hon.3238.
13. O'Brien, S. M., Lamanna, N., Kipps, T. J., Flinn, I., Zelenetz, A. D., Burger, et al, (2015). A phase 2 study of idelalisib plus rituximab in treatment-naïve older patients with chronic lymphocytic leukemia. Blood, 126(25), 2686–2694. https://doi.org/10.1182/blood-2015-03-630947
14. Kwok, M., Agathanggelou, A., Davies, N., & Stankovic, T. (2021). Targeting the p53 Pathway in CLL: State of the Art and Future Perspectives. Cancers, 13(18), 4681. https://doi.org/10.3390/cancers13184681
15. Wang, J., Liu, W., Zhang, L., & Zhang, J. (2023). Targeting mutant p53 stabilization for cancer therapy. Frontiers in pharmacology, 14, 1215995. https://doi.org/10.3389/fphar.2023.1215995
16. Jiang, L., Malik, N., Acedo, P., & Zawacka-Pankau, J. (2019). Protoporphyrin IX is a dual inhibitor of p53/MDM2 and p53/MDM4 interactions and induces apoptosis in B-cell chronic lymphocytic leukemia cells. Cell Death Discovery, 5. https://doi.org/10.1038/s41420-019-0157-7.
17. Duffy, M., Synnott, N., O'Grady, S., & Crown, J. (2020). Targeting p53 for the treatment of cancer.. Seminars in cancer biology. https://doi.org/10.1016/j.semcancer.2020.07.005.

18. Tonino, S., Mulkens, C., Laar, J., Derks, I., Suo, G., Boer, et al, (2015). Induction of TAp73 by platinum-based compounds to overcome drug resistance in p53 dysfunctional chronic lymphocytic leukemia. Leukemia & Lymphoma, 56, 2439 - 2447. https://doi.org/10.3109/10428194.2014.996751.

TRADITIONAL AND NONTRADITIONAL CARDIOVASCULAR RISK FACTORS IN CHRONIC KIDNEY DISEASE: AN INTRODUCTION

Eneida Hoxha, Somida Kuka, Ledio Collaku, Pandush Pojani, Xhesika Habilaj, Margarita Resuli Gjata
University Hospital Center "Mother Theresa", Department of Internal Medicine, Tirana, Albania
Correspondent E-mail: eneida_hoxha@yahoo.com

Abstract

Chronic kidney disease is associated with a significantly elevated risk of cardiovascular morbidity and mortality. While traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia play a critical role, non-traditional risk factors unique to Chronic kidney disease further contribute to this heightened risk. This abstract explores both traditional and non-traditional cardiovascular risk factors in Chronic kidney disease. Traditional risk factors in Chronic kidney disease include hypertension, diabetes mellitus, dyslipidemia, and smoking. These factors accelerate the progression of atherosclerosis and increase the likelihood of cardiovascular events and are intricately linked to Chronic kidney disease pathophysiology, impacting significantly cardiovascular health. The interplay between traditional and non-traditional risk factors is complex. For instance, Chronic kidney disease -related mineral and bone disorders contribute to vascular calcification, which independently predicts adverse cardiovascular outcomes. Similarly, chronic inflammation, common in Chronic kidney disease, promotes atherosclerosis and endothelial dysfunction, further heightening cardiovascular risk. Understanding the collective impact of traditional and non-traditional risk factors is crucial for effective cardiovascular risk stratification and management in Chronic kidney disease patients. Cardiovascular risk assessment tools tailored specifically for Chronic kidney disease populations should encompass both traditional and non-traditional risk markers. Moreover, interventions targeting these multifaceted risk factors, such as optimal blood pressure control, glycemic management, lipid-lowering therapies, and novel Chronic kidney disease -specific treatments, are imperative to mitigate cardiovascular risk in this vulnerable population.

In conclusion, Chronic kidney disease is characterized by a distinct cardiovascular risk profile that extends beyond traditional risk factors. Non-traditional risk factors associated with Chronic kidney disease pathophysiology significantly contribute to cardiovascular morbidity and mortality. Future research should focus on elucidating the mechanisms underlying these non-traditional factors and developing targeted interventions to improve cardiovascular outcomes in Chronic kidney disease patients.

Keyword: Chronic kidney disease, Traditional risk factors, Nontraditional risk factors, Cardiovascular disease.

FAKTORËT TRADICIONALË DHE JO-TRADICIONALË TË RREZIKUT KARDIOVASKULAR NË SËMUNDJEN RENALE KRONIKE: NJË HYRJE

Abstrakt

Sëmundja Renale Kronike lidhet me një rrezik të rëndësishëm të sëmundshmërisë dhe vdekshmërisë kardiovaskulare. Ndërsa faktorët tradicionalë të rrezikut kardiovaskular si hipertensioni, diabeti dhe dislipidemia luajnë një rol kritik, faktorët e rrezikut jo-tradicionalë të veçantë për Sëmundjen Renale Kronike kontribuojnë më tej në këtë rrezik të rritur. Ky abstrakt eksploron të dy faktorët tradicionalë dhe jo-tradicionalë të rrezikut kardiovaskular në Sëmundjen Renale Kronike. Faktorët tradicionalë të rrezikut në Sëmundjen Renale Kronike përfshijnë hipertensionin, diabetin mellitus, dislipideminë dhe duhanpirjen. Këta faktorë përshpejtojnë progresionin e aterosklerozës dhe rrisin mundësinë e ngjarjeve kardiovaskulare. Megjithatë, Sëmundja Renale Kronike shoqërohet me faktorë rreziku shtesë jo-tradicionalë si: çrregullimet minerale dhe kockore, inflamacionin, stresin oksidativ, aneminë, toksinat uremike dhe kalcifikimin vaskular. Njohja këtyre faktorëve, është e rëndësishme për vlerësimin sa më të plotë të riskut kardiovaskular, stadifikimin dhe menaxhimin e pacientëve me Sëmundje Renale Kronike. Mjetet e vlerësimit të riskut kardiovaskular të përshtatura specifikisht për këtë grup popullate duhet të përfshijnë si shënuesit tradicionalë ashtu edhe ata jo-tradicionalë. Për më tepër, ndërhyrjet tek këta faktorë rreziku të shumëfishtë, si kontrolli optimal i shifrave të tensionit arterial, menaxhimi i glicemisë, terapitë për uljen e lipideve dhe trajtimet e reja specifike për Sëmundjen Renale Kronike, janë të domosdoshme për të zvogëluar riskun kardiovaskular në këtë grup vulnerabel popullsie.
Si përfundim, Sëmundja Renale Kronike karakterizohet nga një profil i vecantë rreziku kardiovaskular që shkon përtej faktorëve tradicionalë të riskut. Faktorët e rrezikut jo-tradicionalë të lidhur me fizpatologjinë e SRK kontribojnë në mënyrë të konsiderueshme në morbiditetin dhe mortalitetin kardiovaskular. Hulumtimet e ardhshme duhet të përqëndrohen në zbulimin e këtyre mekanizmave fizpatologjikë të këtyre faktorëve dhe në zhvillimin e ndërhyrjeve të duhura për të përmirësuar rezultatet kardiovaskulare tek pacientët me Sëmundje Renale Kronike.

Fjalë kyçe: Sëmundja Renale Kronike; Faktorët tradicionalë të rrezikut; Faktorët jo-tradicionalë të rrezikut; Sëmundja kardiovaskulare.

Introduction

Chronic kidney disease is increasingly recognized as a global public health problem(1) imposing huge medical and financial burdens on societies and health care systems with an estimated prevalence of 13.4% globally (2). Projections made by the global health burden of disease epidemiologists forecast that in 2040, Chronic kidney disease will be the 5th disease in rank responsible for death in the world.(3) In the 2012 KDIGO, defined Chronic kidney disease as abnormalities of kidney structure or function present for ≥3 months, with implications for health (4). In clinical practice, the main diagnostic criteria for Chronic kidney disease are the presence of an eGFR below 60 mL/min/1.73 m^2, and/or elevated albuminuria, i.e. UACR over 30 mg/g. Cardiovascular (CV) death in patients with CKD prevents these patients from reaching kidney failure (stage G5, i.e., the stage where dialysis and renal transplantation are needed) (5).

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in chronic kidney disease (CKD). CVD mortality risk doubles and triples in CKD stages 3 and 4, respectively (6). This relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other (8,9) Indeed, the heart and kidney are inextricably linked, as exemplified by the cardiorenal syndrome, whereby dysfunction of one organ induces and advances dysfunction in the other (9,10).

In general, in addition to traditional risk factors, two major mechanisms are thought to contribute to the development of CVD in CKD. As renal function deteriorates, non-traditional risk factors play an increasing role in both glomerular filtration rate (GFR) loss and cardiovascular damage. On the one hand, the kidney can release hormones (11-13), enzymes, and cytokines (14,15) in response to kidney injury or kidney insufficiency, which leads to characteristic changes in the vasculature. On the other hand, CKD-associated mediators as well as hemodynamic alterations contribute to cardiac damage,(16) as discussed in the following sections. Understanding cardiovascular risk factors in chronic kidney disease is essential because these patients often face therapeutic nihilism, where appropriate modification and intervention of risk factors is lacking despite awareness of their high cardiovascular risk, therefore, educational efforts are needed to bridge this therapeutic gap. Identifying these risk factors is crucial for the prevention and treatment of chronic heart disease in CKD patients.

In this review, we will focus on whether or not early CKD is an important risk factor for the presence, severity, and progression of CVD. Specifically, we will examine both traditional and novel risk factors for both CKD and CVD and how they relate to each other (figure 1,2).

Figure 1: Changing Cardiovascular Disease Risk in Progressing Chronic Kidney Disease

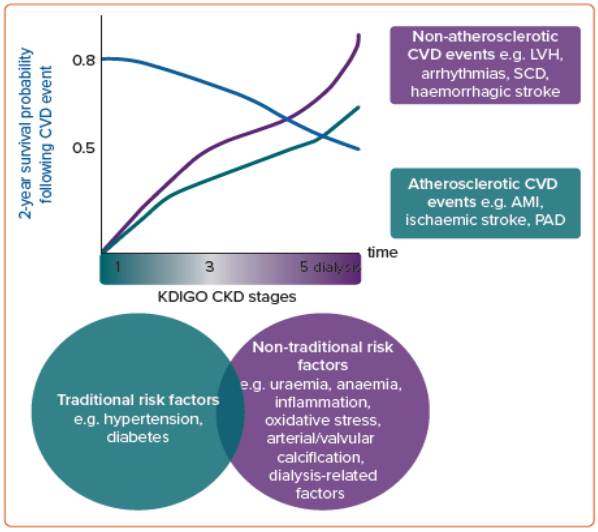


Figure 1: Warrens H, Banerjee D, Herzog Ch, Cardiovascular complications of chronic kidney disease: an indroduction;https://doi.or/10.15420/ecr.2021.54

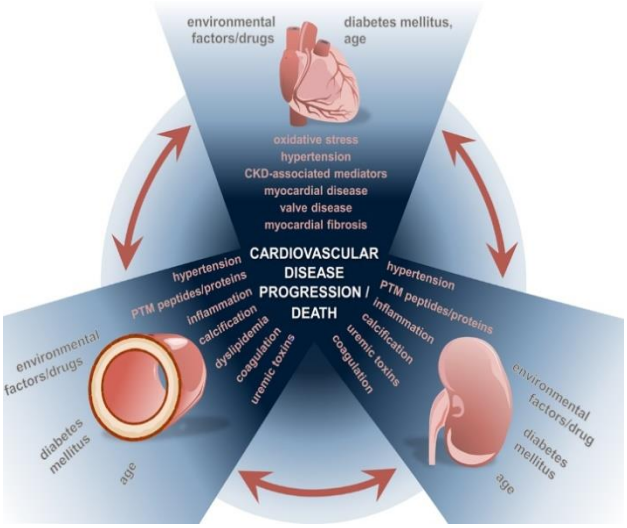


Figure 2: Jankowski J, Floege J, Fliser D, Bohm M, Marx J, Cardiovascular Disease in Chronic Kidney Disease, Pathophysiological Insights and Therapeutic Options https://doi.org/10.1161/CIRCULATIONAHA.120.050686Circulation. 2021;143:1157–117

Traditional cardiovascular risk factors

Traditional cardiovascular risk factors are highly prevalent in patients with CKD, and their contribution to atherosclerotic vascular disease is particularly important in earlier CKD stages (17). The number of cardiovascular risk factors appears to correlate with the severity of kidney dysfunction. Among others, hypertension, insulin resistance/diabetes, dyslipidemia, and smoking contribute not only to atherosclerotic cardiovascular and cerebrovascular sequelae but also to CKD progression because of their effect on large (e.g., kidney artery stenosis) and smaller (e.g., nephrosclerosis) kidney vessels (18). High blood pressure, glucose, and lipid levels, as well as tobacco use, can aggressively be modified.

Hypertension: Hypertension is both a cause and a consequence of CKD. In CKD, impaired kidney function leads to sodium and water retention, volume expansion, and activation of the renin-angiotensin-aldosterone system (RAAS), all of which contribute to hypertension. Conversely, hypertension accelerates the progression of CKD by increasing intraglomerular pressure and promoting renal injury. Additionally, uncontrolled hypertension is a major risk factor for CVD, including coronary artery disease, heart failure, and stroke (4,14,17).

Dyslipidemia: Dyslipidemia is common in CKD and is characterized by elevated levels of triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol, and often normal to mildly elevated levels of low-density lipoprotein (LDL) cholesterol. Dyslipidemia in CKD is multifactorial and is influenced by factors such as inflammation, oxidative stress, insulin resistance, and altered lipid metabolism. Dyslipidemia contributes to the development and progression of atherosclerosis, increasing the risk of coronary artery disease and other cardiovascular events (4,6).

Diabetes Mellitus: Diabetes mellitus is a leading cause of CKD and is associated with a significantly increased risk of CVD. In individuals with both diabetes and CKD, the combination

of renal impairment and metabolic abnormalities further amplifies cardiovascular risk. Diabetes accelerates the progression of CKD through various mechanisms, including hyperglycemia-induced renal injury, activation of inflammatory pathways, and oxidative stress. Moreover, individuals with diabetes are prone to developing microvascular and macrovascular complications, including diabetic nephropathy and coronary artery disease (4,14,18).

Smoking: Smoking is a well-established cardiovascular risk factor and is particularly detrimental to individuals with CKD. Smoking not only increases the risk of atherosclerosis and cardiovascular events but also accelerates the decline in kidney function. Smoking cessation is therefore essential for reducing cardiovascular risk and slowing the progression of CKD (6).

Obesity: Obesity is prevalent in individuals with CKD and is associated with insulin resistance, dyslipidemia, hypertension, and chronic inflammation, all of which contribute to cardiovascular risk. Obesity-related metabolic abnormalities and systemic inflammation promote endothelial dysfunction, atherosclerosis, and left ventricular hypertrophy, further increasing the risk of CVD in CKD (4,14,18).
Management of traditional cardiovascular risk factors is essential in individuals with CKD to reduce the burden of CVD and improve outcomes. This includes lifestyle modifications (such as dietary changes, regular exercise, smoking cessation, and weight management) as well as pharmacological interventions (such as antihypertensive agents, lipid-lowering medications, and glucose-lowering therapies in individuals with diabetes). Additionally, close monitoring and early intervention for cardiovascular risk factors are crucial components of CKD care to optimize cardiovascular health and reduce the risk of adverse cardiovascular events (17,18).

Non-traditional cardiovascular risk factors

This article has focused attention on nontraditional cardiac risk factors that are particularly relevant to patients with CKD, including decreased hemoglobin levels, microalbuminuria, increased inflammation and oxidative stress, and abnormalities in bone and mineral metabolism. Moreover, the mechanisms by which these nontraditional risk factors contribute to cardiovascular disease are numerous. However, toxic metabolites produced by uremia in chronic kidney disease as well as conditions that alter the metabolism of chemical elements, such as calcium and phosphorus, account for the excess CVD in patients with CKD, and are known as non-traditional or new risk factors (19). These non-traditional risk factors play a significant role in the development and progression of CVD in CKD patients. We mention some of them:

Renal failure per se: Newly acquired evidence points to a strong, independent relationship between low eGFR and mortality risk, CV events and hospitalization (20). The mechanisms behind the process of progressive renal function deterioration's acceleration of the atherogenic process are not well known. However, the presence and severity of multiple novel CKD risk factors, including inflammation, oxidative stress, vascular calcification and accumulation of advanced glycation end products (AGEs) increases. Many other accumulating solutes for uremic retention, for example, ADMA, guanidine, homocysteine, indoxyl sulfate and p-cresol, could have a proatherogenic effect (21).

Inflammation: Inflammation is a key process observed in patients with CKD, and CKD is considered a systemic inflammatory disease with many causes (21, 22) and has been shown to predict the long-term risk of developing CKD (22).
Chronic inflammation is characterized by the persistent effect of a causative stimulus, destroying cells and tissue and having a deteriorating effect on the body. In later stages of CKD, the systemic concentrations of both pro- and anti-inflammatory cytokines are significantly higher as production has increased, coupled with decreased renal clearance (21). Inflammation, the effects of local inflammatory stimuli such as oxidation products, end advanced glycosylation products and chronic infective processes modify blood vessels in the sense of atherosclerosis development. These changes benefit proatherogenic adhesion molecule production, for example, intercellular adhesion molecule1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), growth factor, as well as chemokine (such as IL-6, long pentraxin 3 (PTX3), S-albumin, TNF and white blood cell count). Such inflammatory intermediates encourage the synthesis of acute phase proteins such as C-reactive protein (CRP) (23), which leads to endothelial dysfunction, which is usually defined as reduced vasodilatation capability, which again creates early atherosclerosis occurrence predisposition. Aside from that, the proinflammatory IL-6 mark is increased in ESRD patients but is also an independent mortality predictor in patients on dialysis (24).

Endothelial dysfunction: There is evidence that suggests that the endogenic inhibitor of NO, ADMA, has a significant role in the origin and occurrence of CVD and mortality in dialysis patients. NO deficit and ADMA accumulation promote endothelial dysfunction, vasoconstriction, and arterial thrombosis (20, 22).

Malnutrition and protein-energy wasting (PEW): A marked connection between malnutrition, increased levels of CRP and atherosclerosis is well known, although the precise mechanisms of their synergistic effects on the organism are not known (25).
Oxidative stress: CKD patients experience increased oxidative stress due to reduced antioxidant defenses and accumulation of uremic toxins. Oxidative stress contributes to endothelial dysfunction, vascular inflammation, and accelerated atherosclerosis. CKD patients have a deficiency in the antioxidant defensive mechanism (because of e.g., reduced vitamin levels, or hypoalbuminemia) and increased pro-oxidant compound activity. One of the most important toxins connected to the uremic environment and connected to oxidative stress and inflammation stage and the presence of inflammation biomarkers is β2-microglobulin (16,24).
Hyperparathyroidism: PTH is considered a potent uremic toxin that has a detrimental effect on myocardial cells. The role of parathormone as a risk factor in the development of uremic cardiomyopathy is known. Important research results show in conclusion that a small level of vitamin D is associated with CVD in the general population and that a greater concentration of this vitamin may have a positive impact on survival (24).
Cardiovascular calcification: The calcification process frequently starts before the initiation of dialysis treatment. The arterial media, atherosclerotic plaques and heart valves are affected through this cardiovascular process. One of the main signs of medial calcification is arterial stiffness, which is shown clinically through an increased pulse pressure. It is now evident that the burden caused by atherosclerotic calcification is a suitable risk marker for cardiovascular events. In patients in dialysis, valvular calcification leads to a developing stenosis and morbidity that

goes with it, after targeting and affecting the aortic and mitral valves (26). CV calcification can be caused by abnormal calcium and phosphate metabolism and an enduring inflammation as it may by several mechanisms mediate untimely atherosclerosis and premature CVD.

Hyperhomocysteinemia: Homocysteine is a nonprotein sulfur-containing amino acid and may by several mechanisms mediate premature atherosclerosis and CVD. The prevalence of hyperhomocysteinemia in patients with advanced CKD is >90% (27).

Anemia: CKD often develops anemia due to decreased production of erythropoietin by the kidneys. Anemia leads to tissue hypoxia, cardiac remodeling, and an increased cardiac workload. Chronic anemia contributes to left ventricular hypertrophy, diastolic dysfunction, and myocardial ischemia, exacerbating cardiovascular risk (12, 13).

These non-traditional factors interact with conventional cardiovascular risk factors (e.g., hypertension, dyslipidemia) to amplify cardiovascular risk in CKD patients. Addressing these factors requires a comprehensive approach, including optimized CKD management, dietary interventions, control of inflammation and oxidative stress, and targeted therapies to mitigate vascular calcification and uremic toxin accumulation. By understanding and targeting both traditional and non-traditional risk factors, clinicians can improve cardiovascular outcomes and quality of life in CKD patients. Patients with CKD should be considered in the highest-risk group for development of cardiovascular disease (CVD), and aggressive treatment of traditional and nontraditional risk factors should be instituted.

Novel therapeutic approaches

Preventing cardiovascular risk in chronic kidney disease (CKD) requires a comprehensive approach that targets both traditional cardiovascular risk factors and CKD-specific factors. Several novel therapies and emerging strategies are being investigated to reduce cardiovascular risk and improve outcomes in CKD patients. Here are some promising therapies and interventions:

SGLT2 Inhibitors: Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for the treatment of diabetes, have shown remarkable cardiovascular and renal protective effects in CKD patients with or without diabetes. These medications reduce cardiovascular events, slow the progression of CKD, reduce albuminuria progression, the preservation of eGFR, even in advanced CKD stages, and lower blood pressure through mechanisms independent of glucose lowering. Potential mechanisms explaining the beneficial effects of SGLT2 inhibitors in patients with HF or CKD include hemodynamic as well as metabolic effects (28). In addition, SGLT2 inhibitors may selectively reduce interstitial fluid, and this may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics (29).

MRAs: Nonsteroidal mineralocorticoid receptor antagonist reduce the aldosterone-mediated proinflammatory effects that are involved in the fibrotic remodeling processes. The new selective nonsteroidal MRA finerenone also blocks the damaging effects of the overactivated aldosterone system. Finerenone is equally distributed in myocardial and kidney tissue (30).

Novel Lipid-lowering Therapies: Beyond statins, newer lipid-lowering agents such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are being explored for their efficacy in reducing cardiovascular events in CKD patients with dyslipidemia (31).

Mineral and Bone Disorder (MBD) Management: Novel phosphate binders and calcimimetics are being developed to better manage mineral and bone disorders in CKD. These therapies aim to control serum phosphate levels, reduce secondary hyperparathyroidism, and mitigate vascular calcification, which is a major contributor to cardiovascular risk in CKD (26, 27).

Anti-inflammatory Therapies: Targeting inflammation is emerging as a promising approach to reduce cardiovascular risk in CKD. Novel anti-inflammatory agents, such as monoclonal antibodies against interleukin-1 beta (IL-1β) or interleukin-6 (IL-6), are being studied for their potential to lower systemic inflammation and improve cardiovascular outcomes. Omega-3 supplementation has shown anti-inflammatory effects and cardiovascular benefits in CKD populations (24, 25).

Novel Antihypertensive Agents: Agents targeting the renin-angiotensin-aldosterone system (RAAS), or novel mechanisms Endothelin receptor antagonists (ERAs) have been investigated for their potential role in chronic kidney disease (CKD), there is growing interest in their renal effects due to the involvement of endothelin in renal hemodynamics, fibrosis, and inflammation. Endothelin receptor antagonists, by blocking the action of endothelin, may promote renal vasodilation and improve renal blood flow, exert antifibrotic effects by inhibiting endothelin-induced fibroblast proliferation, extracellular matrix deposition, and myofibroblast activation, mitigate inflammation by blocking endothelin-mediated immune cell activation and cytokine release within the kidney, reduce proteinuria. ERAs may help preserve kidney function and delay CKD progression, may provide additional cardiovascular benefits beyond blood pressure control (29, 30, 31).

Precision Medicine: Personalized treatment approaches based on genetic and molecular profiling may help identify individuals at higher cardiovascular risk and tailor therapies accordingly. Biomarker-guided strategies can optimize cardiovascular risk management in CKD.

While these novel therapies hold promise for reducing cardiovascular risk in CKD, further research is needed to evaluate their efficacy, safety, and long-term benefits specifically in CKD populations. Comprehensive management strategies that address both traditional and CKD-specific cardiovascular risk factors remain essential for improving outcomes and quality of life in CKD patients at high risk for cardiovascular events.

Conclusion

CVD is very common in CKD, and vice versa. The presence of each condition promotes the incidence and progression of the other. Despite the high prevalence, morbidity, and mortality of these comorbid conditions, there are significant limitations to our current knowledge and management of this vulnerable group. As CKD progresses and the incidence of CVD rises, we have less knowledge and fewer management options. The complexity of these comorbid conditions necessitates a multidisciplinary approach to improve patient-centered care. It's important to note that while these novel therapies hold promise, further research and clinical trials are needed to establish their efficacy, safety, and long-term benefits specifically in CKD populations. Comprehensive management of cardiovascular risk in CKD requires a personalized approach that addresses individual patient factors and optimizes multifactorial interventions to improve outcomes and quality of life, requiring a multidisciplinary care model that includes nephrologists, cardiologists, internists, endocrinologists, dieticians, and other specialists.

References

1. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. **Lancet.** 2013; 382:158–169. doi: 10.1016/S0140-6736(13)60439-0

2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. **PLoS One.** 2016;11:e0158765. doi: 10.1371/journal.pone.0158765
3. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC, Friedman J, He J, Heuton KR, Holmberg M, Patel DJ, Reidy P, Carter A, Cercy K, Chapin A, Douwes-Schultz D, Frank T, Goettsch F, Liu PY, Nandakumar V, Reitsma MB, Reuter V, Sadat N, Sorensen RJD, Srinivasan V, Updike RL, York H, Lopez AD, Lozano R, Lim SS, Mokdad AH, Vollset SE, Murray CJL. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 2018; 392:2052–2090.
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150
5. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659–663.
6. Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;74:1823–38.
7. Watanabe H, Watanabe T, Sasaki S, et al. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata Preventive Medicine study. Am Heart J 2009;158:629–36.
8. Damman K, Valente MAE, Voors AA, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455–69.
9. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–39.
10. Zannad F, Rossignol P. Cardiorenal syndrome revisited. Circulation 2018;138:929–44.
11. Buglioni A, Burnett JCPathophysiology and the cardiorenal connection in heart failure. Circulating hormones: biomarkers or mediators.Clin Chim Acta. 2015; 443:3–8. doi: 10.1016/j.cca.2014.10.027
12. Briet M, Barhoumi T, Mian MO, Sierra C, Boutouyrie P, Davidman M, Bercovitch D, Nessim SJ, Frisch G, Paradis P, et al. Effects of recombinant human erythropoietin on resistance artery endothelial function in stage 4 chronic kidney disease.**J** Am Heart Assoc. 2013; 2:e000128. doi: 10.1161/JAHA.113.000128
13. Onal EM, Sag AA, Sal O, Yerlikaya A, Afsar B, Kanbay M. Erythropoietin mediates brain-vascular-kidney crosstalk and may be a treatment target for pulmonary and resistant essential hypertension.Clin Exp Hypertens. 2017; 39:197–209. doi: 10.1080/10641963.2016.1246565
14. Nasrallah R, Hassouneh R, Hébert RL. PGE2, kidney disease, and cardiovascular risk: beyond hypertension and diabetes.J Am Soc Nephrol. 2016; 27:666–676. doi: 10.1681/ASN.2015050528
15. Tan K, Sethi SK. Biomarkers in cardiorenal syndromes.Transl Res. 2014; 164:122–134. doi: 10.1016/j.trsl.2014.04.011

16. Fujii H, Goto S, Fukagawa M. Role of uremic toxins for kidney, cardiovascular, and bone dysfunction.**Toxins.** 2018; 10:202–220. doi: 10.3390/toxins10050202
17. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. PLoS One. 2018;13:e0192895. doi: 10.1371/journal.pone.0192895
18. Centers for Disease Control and Prevention. National Chronic Kidney Disease Fact Sheet, 2017.Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.
19. Culleton B.F., Larson M.G., Parfrey P.S., Kannel W.B., Levy D. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: A prospective study. Am. J. Med. 2000;109:1–8.
20. Tonelli M, Pfeffer MA. Kidney disease and cardiovascular risk. Annual Review of Medicine. 2007;58:123-139
21. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, et al; European Renal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA). The systemic nature of CKD. Nat Rev Nephrol. 2017; 13:344–358. doi: 10.1038/nrneph.2017.52
22. Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M, Wolf M, Reilly M, Ojo A, Townsend RR, et al; CRIC Study Investigators. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD: findings from the CRIC Study. Am J Kidney Dis. 2019; 73:344–353. doi: 10.1053/j.ajkd.2018.09.012
23. Tseng JR, Lin CW, Chen SH, Yen TH, Lin PY, Lee MH, Yen TC. Clinical usefulness of ^{18}F-FDG PET/CT for the detection of infections of unknown origin in patients undergoing maintenance hemodialysis. Journal of Nuclear Medicine. 2015;56(5):681-687. DOI: 10.2967/jnumed.114.151696
24. Pisetkul C, Chanchairujira K, Chotipanvittayakul N, Ong-Ajyooth L, Chanchairujira T. Malnutrition-inflammation score associated with atherosclerosis, inflammation and short-term outcome in hemodialysis patients. Journal of the Medical Association of Thailand. 2010;93(Suppl. 1):S147-S156
25. Stenvinkel P, Heimbürger O, Paultre F, Diczfalusy U, Wang T, Berglund L. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney International. 1999;55:1899-1911
26. Custódio MR, Koike MK, Neves KR, dos Reis LM, Graciolli FG, Neves CL, Batista DG, Magalhães AO, Hawlitschek P, Oliveira IB, Dominguez WV, Moysés RM, Jorgetti V. Parathyroid hormone and phosphorus overload in uremia: Impact on cardiovascular system. Nephrology, Dialysis, Transplantation. 2012;27(4):1437-1445. DOI: 10.1093/ndt/gfr447.
27. Ye Z, Zhang Q, Li Y, Wang C, Zhang J, Ma X, Peng H, Lou T. High prevalence of hyperhomocysteinemia and its association with target organ damage in chinese patients with chronic kidney disease. Nutrients. 2016;8(10):645.

28. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. ESC Heart Fail**.** 2019; 6:927–935. doi: 10.1002/ehf2.12505.
29. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia**.** 2018; 61:2108–2117. doi: 10.1007/s00125-018-4670-7
30. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney Int 2019; 96:302-319.
31. Hajar R. PCSK 9 Inhibitors: A short history and a New Era of Lipid –lowering Therapy. Heart Views. 2019 Apr- Jun;20(2):74-75.

ARTERIAL HYPERTENSION: THE PRINCIPLES OF ITS TREATMENT ACCORDING TO THE GUIDELINES OF THE EUROPEAN ASSOCIATION OF HYPERTENSION - 2023

Pandush Pojani, Eneida Hoxha, Somida Kuka, Ledio Çollaku, Kristian Bitraj, Margarita Gjata Resuli
Service of Internal Medicine & HTN, University Hospital Center "Mother Teresa", Tirana, Albania

Correspondent E-mail: pandushpojani@hotmail.com;

Abstract

Arterial hypertension remains the most common, easily identifiable, and reversible risk factor for coronary artery disease, myocardial infarction, heart failure, ischemic and hemorrhagic cerebrovascular accidents, decline in cognitive functions, renal failure, aortic dissection and diseases of the peripheral arteries. The asymptomatic nature of arterial hypertension in a significant part of patients delays diagnosis, makes it more difficult for patients to adapt to lifestyle modification, regular medication and periodic follow-up. At the time of diagnosis, the assessment of organ damage caused by hypertension, assessment of cardio-vascular risk and other associated diseases should be done. On the basis of arterial pressure values, organ damage caused by hypertension, assessment of cardiovascular risk, associated diseases, the age group of the patient, the hypertension treatment strategy will be built, where the number of drugs to be started, the type of treatment will be determined of them, the arterial pressure values that must be reached and the time that must be reached are determined. In hypertensive patients, the reduction of arterial pressure values to the specified values significantly reduces major cardiovascular events such as myocardial infarction, ischemic and hemorrhagic cerebrovascular accidents, heart failure and mortality from all causes also shows a protective effect against asymptomatic heart damage and kidneys and prevents the decrease of cognitive functions and dementia. Drug treatment of hypertension with two or more drugs combined in one tablet is recommended.

Keywords: Target organs, cardiovascular risk, antihypertensive therapy.

HIPERTENSIONI ARTERIAL: PRINCIPET E TRAJTIMIT SIPAS UDHERREFYESVE TE SHOQATES EUROPIANE TE HIPERTENSIONIT - 2023

Abstrakt

Hipertensioni arterial mbetet faktori i rrezikut më i zakonshëm, lehtësisht i identifikueshëm, dhe i rikthyeshëm për sëmundjet e arterieve koronare, infarktin e miokardit, insufiçiencën kardiake, aksidentet cerebrovaskulare ishemike dhe hemoragjike, rënien e funksioneve konjitive, sëmundjen renale, diseksionin e aortës dhe sëmundjen e arterieve periferike. Natyra asimptomatike e hipertensionit arterial në një pjesë të konsiderueshme të pacientëve, vonon diagnozën, e bën më të vështirë përshtatjen e pacientëve me modifikimin e mënyres së jetesës, marrjen e rregullt të mjekimit dhe ndjekjen periodike të tyre. Në momentin e diagnostikimit

duhet bërë vleresimi i dëmtimit të organeve target, të shkaktuar nga hipertensioni, vlerësimi i riskut kardio-vaskular dhe sëmundjet e tjera shoqëruese. Mbi bazën e vlerave të presionit arterial, dëmtimit të organeve të shkaktura nga hipertensioni, vlerësimit të riskut kardio-vaskular, sëmundjeve shoqëruese, grupmosha e pacientit, do të ndërtohet strategjia e trajtimit të hipertensionit, ku përcaktohet numri i barnave që do të fillohet trajtimi, lloji i tyre, përcaktohen vlerat e presionit arterial që duhet të arihen dhe koha që duhet të arihen. Në pacientët hipertensivë, ulja e vlerave të presionit arterial në vlerat e përcaktuara, ul në mënyrë të rëndësishme eventet madhore kardiovaskulare: si infarkti i miokardit, aksidentet cerebrovaskulare ishemike dhe hemoragjike, insufiçiencën kardiake dhe vdekshmërinë nga të gjitha shkaqet, gjithashtu tregon efekt mbrojtës ndaj dëmtimeve asimptomatike të zemrës dhe veshkave dhe parandalon uljen e fuksioneve kognitive dhe demencës. Rekomandohet trajtimi medikamentoz i hipertensionit me dy ose më shumë barna të kombinuara në një tabletë.

Fjalë kyçe: Organet target, risku kardio-vaskular, antihipertensivët.

Introduction

Hypertension is the most prevalent cardiovascular disorder in the world, and it remains a global problem and the situation is getting worse. The world's population is "aging" and age is the most common risk factor for hypertension. Most hypertensive subjects are diagnosed with primary or essential hypertension. Essential hypertension is a hereditary syndrome that reflects a series of pathological abnormalities, which lead independently or together to an increase in blood pressure. Although secondary causes exists in a small percentage of hypertensive subjects, again they represent a large number of patients. Secondary forms of hypertension account for only a small part of the overall prevalence of hypertension, which is mainly due to primary hypertension. However, their true prevalence is not precisely known, because the available data may be confounded by the selection of studies reported in the literature, the number of undiagnosed cases, and the different definition of secondary forms of hypertension (1,2).
Hypertension is a major cardiovascular risk factor. So, ischemic heart disease is twice as frequent in these subjects, while in 60% of cases with heart failure the only cause is considered high blood pressure, while it’s responsible for 50% of cases with Ischemic Insult and in over 80% of cases with hemorrhagic stroke (8). Estimation of total cardiovascular risk is easy in specific subgroups of patients, such as those with a history of existing cardiovascular disease, diabetes melitus, coronary artery disease, or single highly elevated risk factors. In all these situations, the total cardiovascular risk is high or very high, requiring intensive measures that reduces this risk (9). However, a large number of patients with hypertension do not belong to any of the above categories and their identification in low, moderate, high or very high risk requires the use of models to estimate the total cardiovascular risk, so we are able to judge the therapeutic method in accordance with them (9). A further importance is the identification of asymptomatic target organ damage, while asymptomatic alterations associated with hypertension in some organs indicate progression in the installation of cardiovascular disease, which significantly increases the risk beyond that caused by the simple presence of risk factors (1).

Epidemiology

Hypertension is the most prevalent cardio-vascular disorder in the world and according to the WHO, it affects 1.28 billion adults aged 30–79 years worldwide (1), two-thirds living in low- and middle-income countries. The average prevalence of hypertension in adults aged 30-79 years has been reported to be 34% in men and 32% in women (2). In younger ages (<50 years), hypertension is more prevalent in men, while in older age categories (>65 years) it is more prevalent in women(3,4). Systolic arterial pressure increases progressively with age while diastolic arterial pressure increases until the age of 50-60 years, followed by a short period of stability and then we have a subsequent slight decrease. This results in an increase in the difference between systolic and diastolic arterial pressure with age (3).

Definition and classification of hypertension

According to previous 2018 European(5,6,7) and current international guidelines, hypertension is defined based on repeated office values of systolic arterial pressure above 140 mmHg and/or diastolic above 90 mmHg. This definition is arbitrary and has mainly a practical purpose to simplify the diagnosis and decisions for the management of hypertension. In this context, the above threshold values of arterial pressure correspond to the level at which the benefits of intervention exceed those of inaction.

Table 1. Arterial pressure staging

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and	80-84
High normal	130-139	and / or	85-89
Stage 1 hypertension	140-159	and / or	90-99
Stage 2 hypertension	160-179	and / or	100-109
Stage 3 hypertension	≥180	and / or	≥110
Isolated systolic hypertension	≥140	and	<90
Isolated diastolic hypertension	<140	and	≥90

In addition to the staging of hypertension, which is based on arterial pressure values, we also distinguish the stages of hypertension as follows (1):

Stage 1 : Uncomplicated hypertension (without organ damage caused by hypertension or cardiovascular disease, but including chronic kidney disease stages 1 and 2)

Stage 2 : Presence of organ damage caused by hypertension or stage 3 chronic kidney disease or diabetes.

Stage 3 : Presence of cardiovascular disease or stage 4 or 5 chronic renal disease.

Hypertension and cardiovascular risk assessment

There is a continuous relationship between increased arterial pressure and the risk of cerebrovascular accidents, coronary artery disease, heart failure, and the development and progression of chronic kidney disease (8). This applies to all ages and ethnic groups. It is recommended to evaluate the total cardiovascular risk in every hypertensive patient because of its importance in the management of hypertension (9).

Table 2. Cardiovascular risk according to stage and stage of hypertension

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors[a]	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥4	Very high risk	Very high risk	Very high risk	Very high risk

	<50 years	60–69 years	≥70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

Complementary risk estimation in Stage 1 with SCORE2/SCOR2-OP

Abbreviations: CKD chronic kidney disease, CVD cardiovascular disease, HMOD hypertension-mediated organ damage.

Treatment

Lifestyle modification

Adapting a healthy cardiac lifestyle is an important approach to prevent or delay the onset of hypertension, to reduce high blood pressure values, to reduce cardiovascular risk, increase the effectiveness of drug treatment and reduce the number of necessary drugs for blood pressure control(10). The most important and effective lifestyle interventions that have shown a reduction in cardiovascular morbidity and mortality are weight loss, salt reduction, increased potassium intake, regular physical activity, reduced alcohol consumption, smoking cessation, improvement of stress control, reducing exposure to noise and polluted air. Lifestyle modification should be done at every stage or stage of hypertension (11).

Drug treatment

Antihypertensive drugs

Blockers of the renin-angiotensin system:

- Angiotensin-converting enzyme inhibitors (ACEi) such as enalapril, ramipril
- Angiotensin receptor blockers (ARBs) such as valsartan, olmesartan
- Renin inhibitors such as aliskiren, which is no longer used in some European countries.

Calcium channel blockers (CCBs)

- Dihydropyridine CCBs such as amlodipine, lercanidipine
- Non-dihydropyridine CCBs such as verapamil, diltiazem

Diuretics

- Thiazides / thiazides like (T/TL Diuretic) such as hydrochlorothiazide / chlorthalidone, indapamide
- Loop Diuretics such as furosemide, torasemide
- Potassium sparing agents such as amiloride, triamterene

Mineralocorticoid receptor antagonists (MRAs) such as spironolactone, eplerenone
Beta blockers (BBs) such as metoprolol bisoprolol
Alpha 1 blockers such as doxazosin
Centrally acting drugssuch as methyldopa, moxonidine
Vasodilators such as hydralazine, nitrates
Angiotensin and neprilysin receptor inhibitors (ARNIs) such as valsartan / sacubitril which is approved as an antihypertensive in China and Japan
The following five classes are recommended as first-line drugs for the treatment of hypertension, ACEi, ARB, CCB, T/TL diuretics, BB(9). The selection of these five classes is based on the following criteria(1):

1. A proven ability to lower arterial pressure as monotherapy
2. Given that they reduce morbidity and mortality
3. A favorable tolerance and safety profile

Selection of drugs for the treatment of hypertension

According to the guidelines of the European Association of Hypertension 2023, for the most efficient treatment of hypertension, it is suggested to follow these recommendations (1):

1. In most patients, the treatment should start with two drugs combined in one tablet to improve the speed, efficiency and predictability in the control of arterial pressure(9,12,13).
2. Although some two-drug combinations may be used, the preferred two-drug combinations should be an ACEi or ARB with a CCB or a thiazide/thiazide-like diuretic(1,9).
3. A beta blocker can be used at any step of the combination with any of the other first-line classes or in special cases(14).
4. Initial monotherapy is recommended for very high-risk patients with normal to high blood pressure as well as for very elderly and physically weak patients. It may also be considered in low-risk patients with stage 1 hypertension, with systolic blood pressure <150 mmHg(1,15).

5. A combination in one tablet containing an ACEi or ARB + CCB + thiazide/thiazide-like diuretic should be used if combinations of two drugs do not achieve arterial pressure control (at maximum tolerated doses) and if BBs are not indicated.
6. Regardless of the initial choice of treatment, in the end most patients should be on combined treatment, using the combination in one tablet when possible.

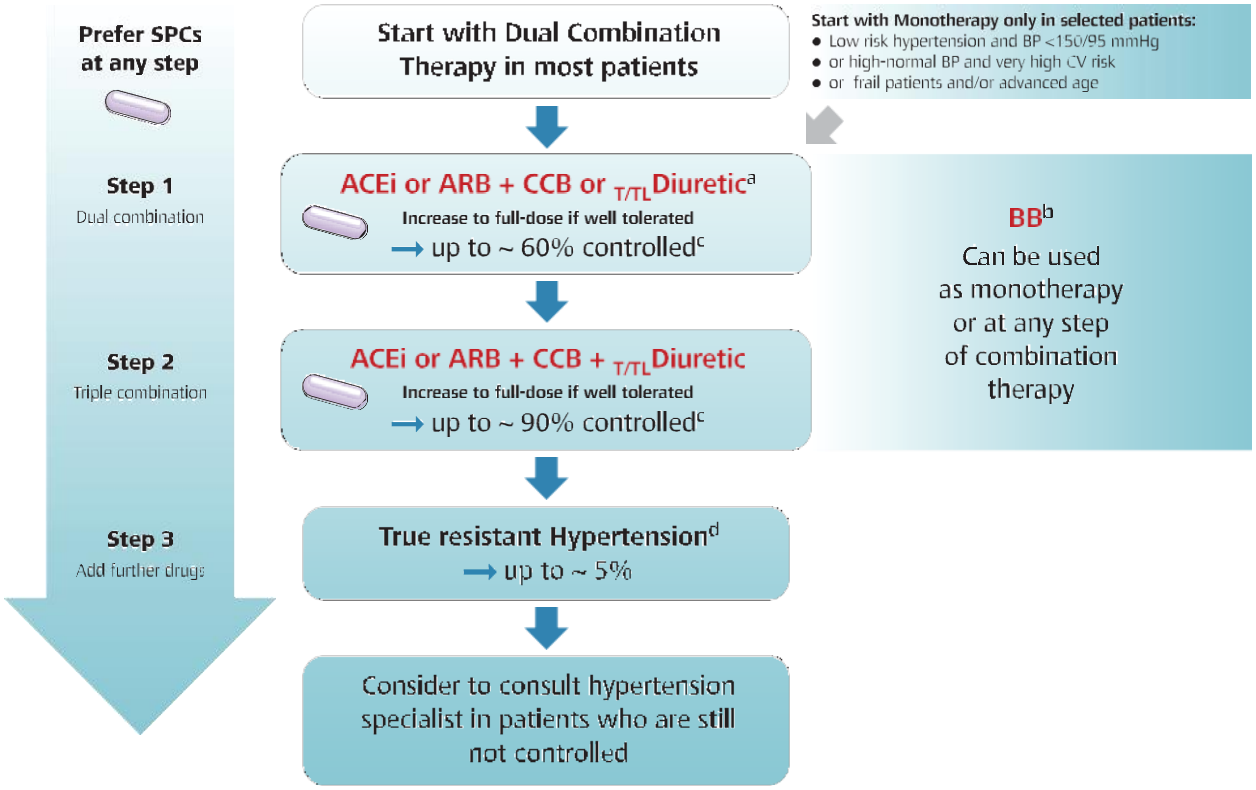
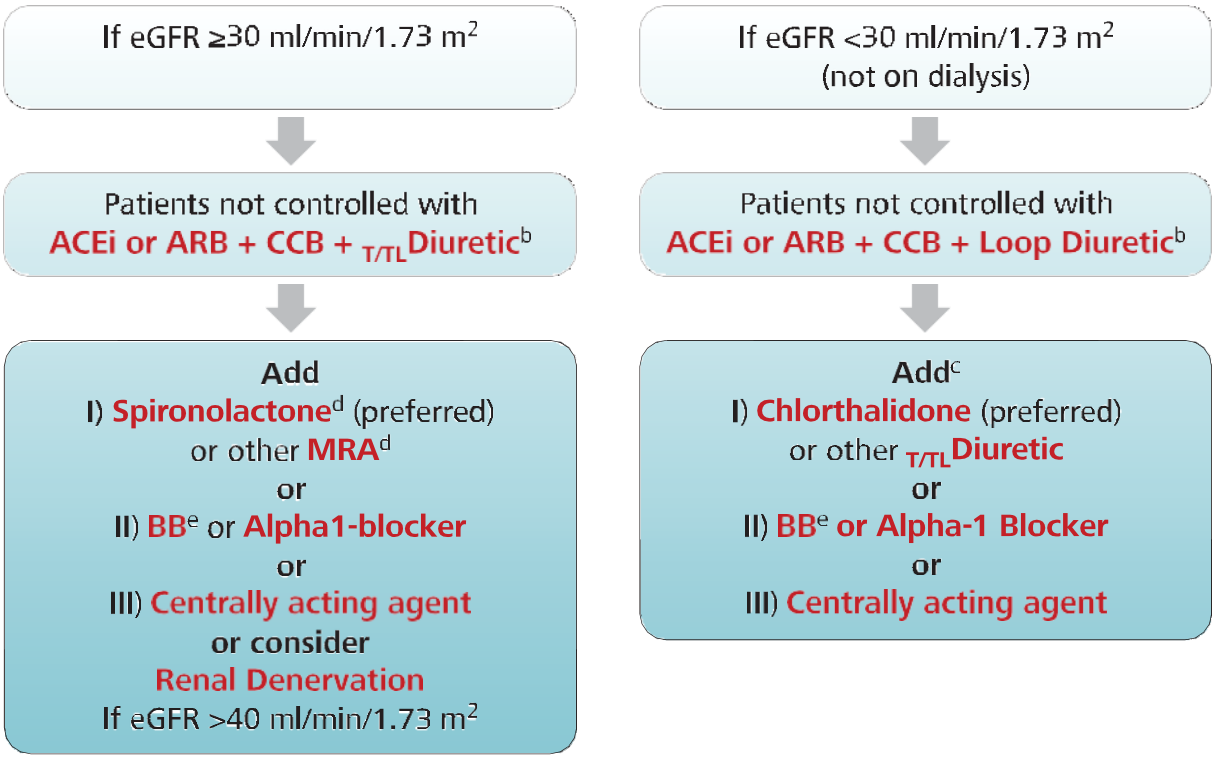


Figure 1. General strategy of arterial pressure treatmentin hypertensive patients

Hypertension resistant to medication

Hypertension is defined as drug-resistant when appropriate lifestyle measures and treatment with optimal or better-tolerated doses of three or more drugs (a thiazide / thiazide-like diuretic, an ACEi or ARB, and a CCB) fail to reduce arterial pressure measured in the office < 140 / 90 mmHg(9). Improper control of arterial pressure must be confirmed by measurements outside the office that show uncontrolled values of arterial pressure during 24 hours (≥ 130 / 80 mmHg). Regular intake of medication and exclusion of secondary hypertension are necessary to determine true resistant hypertension (1).
In patients with resistant hypertension, the fourth line of treatment should be a MRA, spironolactone (16). When MRAs are not tolerated or contraindicated, doxazosin or a centrally acting drug can be used as an alternative (17).

Figure 2. The strategy of reducing arterial pressure in resistant hypertension



If eGFR is <30 ml /min/1.73 m², loop diuretics are the first line instead of thiazide / thiazide-like diuretics in the treatment of hypertension (18).

Renal denervation

Renal denervation can be considered as an alternative treatment of resistant hypertension in patients with eGFR > 40 ml /min/1.73 m² in whom medical control of arterial pressure has not been achieved(19).

Conclusion

Hypertension remains a silent killer. We need to know very well the pathophysiology, its clinic, in order to go as soon as possible to the correct diagnosis, which guides us towards the right treatment, at the right time. This will reduce the complications of hypertension, i.e. damage to the target organs, reducing the cardiovascular morbidity and mortality.

References

1. Mancia G, Kreutz R, Brunstrom M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension. The Task Force for the

management of arterial hypertension of the European Society of Hypertension [published online June 21, 2023]. J Hypertens. doi: 10.1097/ HJH. 0000000000003480.

2. NCD Risk Factor Collaboration (NCD- RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 populationrepresentative studies with 104 million participants. Lancet 2021; 398:957–980.

3. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. Circ Res 2019; 124:1045–1060.

4. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Merz CNB, et al. Sex differences in blood pressure trajectories over the life course. JAMA Cardiol 2020; 5:255–262.

5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension (Dallas, Tex: 1979) 2020; 75:1334–1357.

6. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021; 42:3227–3337.

7. WHO. Guideline for the pharmacological treatment of hypertension in adults. World Health Organization; 2021 Licence: CC BY-NC-SA 30 IGO 2021.

8. Lu S, Bao MY, Miao SM, Zhang X, Jia QQ, Jing SQ, et al. Prevalence of hypertension, diabetes, and dyslipidemia, and their additive effects on myocardial infarction and stroke: a cross-sectional study in Nanjing, China. Ann Transl Med 2019; 7:436.

9. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018; 36:1953–2041.

10. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J2016; 37: 2315-2381.

11. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a metaanalysis. Circulation 2011

12. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. J Hypertens 2014; 32:1708–1715; discussion 1716

13. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31:1281–1357

14. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs - overview and meta-analyses. J Hypertens 2015; 33:1321–1341.

15. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged 75 Years: A Randomized Clinical Trial. Jama 2016; 315:2673–2682.

16. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015; 386:2059–2068.

17. Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JAS, Nogueira AR, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the rehot randomized study (resistant hypertension optimal treatment). Hypertension (Dallas, Tex: 1979) 2018; 71:681–690.

18. Agarwal R, Sinha AD, Cramer AE, Balmes-Fenwick M, Dickinson JH, Ouyang F, et al. Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease. N Engl J Med 2021; 385:2507–2519.

19. Barbato E, Azizi M, Schmieder RE, Lauder L, Bohm M, Brouwers S, et al. Renal Denervation in the Management of Hypertension in Adults. A Clinical Consensus Statement of the ESC Council on Hypertension and the European Association of Cardiovascular Interventions (EAPCI). Eur Heart J 2023; 44:1313–1330.

MELANOMA – THE IMPORTANCE OF DIAGNOSIS AT ANY AGE

Elmijola Lame-Janushaj, Stratis Gabriel, Mario Cobaj
Department of Dermatology and Plastic Surgery
Doctors General Clinic Tirana

Correspondent E-mail: elmijolalame@gmail.com

Abstract
Melanoma is a malignant cutaneous neoplasm characterized by the uncontrolled proliferation of melanocytes. Importantly, melanoma does not exhibit distinct age, sex, or racial predilections, underscoring the need for diligence in the monitoring and early detection of suspicious lesions across all demographics. Dermoscopy, a non-invasive diagnostic technique that allows for enhanced visualization of pigmented skin lesions, plays a pivotal role in the early identification of melanoma. There are presented three cases of melanoma in situ in different groups of ages, emphasising the importance of detecting them in time, surgery excision and follow up. Collaboration of the dermatologist, oncologist and healthcare professionals is very important to defeat the diseases and to lower the morbidity of this malignancy.

Keyword: melanoma, dermoscopy, age, prognosis, follow-up

MELANOMA - RËNDËSIA E DIAGNOSTIKIMIT NË ÇDO MOSHË

Abstrakt
Melanoma është një patologji malinje e lëkurës, e karakterizuar nga një proliferim i pakontrolluar i melanociteve. Melanoma nuk shfaq prirje të dallueshme ndaj moshës, gjinisë apo racës, duke nënvizuar nevojën për monitorim dhe zbulim të hershëm të lezioneve të pigmentuara të lëkurës në të gjitha demografitë. Dermoskopia, një teknikë jo-invazive që lejon vizualizimin e lezioneve të lëkurës, luan një rol të rëndësishëm në identifikimin e hershëm të melanomës. Në këtë artikull janë paraqitur tre raste të melanomës in situ në grupmosha të ndryshme, duke theksuar rëndësinë e zbulimit në kohë të tyre, ekcizionit kururgjikal dhe ndjekje në vazhdimësi. Bashkëpunimi i profesionistëve të kujdesit shëndetsor, dermatolog, onkolog dhe kirurg është shumë i rëndësishëm për të mposhtur patologjinë dhe për të ulur sëmundshmërinë e kësaj neoplazie.

Fjalë kyçe: melanoma, dermoscopia, mosha, prognoza, ndjekja.

Introduction

Melanoma is a malignant cutaneous neoplasm characterized by the uncontrolled proliferation of melanocytes, the pigment-producing cells of the skin. It presents a significant mortality risk due to its propensity for metastasis if not diagnosed and treated in its early stages (1). Importantly, melanoma does not exhibit distinct age, sex, or racial predilections, underscoring the need for diligence in the monitoring and early detection of suspicious lesions across all demographics

(2,3,6,7). Dermoscopy, a non-invasive diagnostic technique that allows for enhanced visualization of pigmented skin lesions, plays a pivotal role in the early identification of melanoma (1). Within this context, the presentation of three cases spanning diverse age groups underscores the pervasive nature of melanoma and the criticality of proactive surveillance and early intervention. Each case serves as a testament to the favourable outcomes achievable through vigilant monitoring and regular dermatologic assessments. By acknowledging the significance of these cases, we can appreciate the crucial impact of continuous follow-up and proactive engagement with dermatologists in mitigating the potential ramifications of melanoma.

Case 1: Youth Melanoma: A 21-year-old male presented with a new, rapidly enlarging pigmented lesion on his forth finger in left hand (Fig 1.1), which was noted by a random visit to dermatologist. Upon dermatologic evaluation and subsequent dermoscopic analysis (Fig1.2), the lesion exhibited concerning features, including irregular pigmentation and asymmetry. A prompt excisional biopsy confirmed the diagnosis of early-stage melanoma. Subsequent histopathologic assessment revealed in situ melanoma, underscored the insidious nature of melanoma progression, even in the absence of overt symptoms or alarming changes. The timely identification of this lesion allowed for a curative surgical resection and a positive prognostic outlook. Continued monitoring and adherence to scheduled follow-up appointments remain integral to ensuring the enduring well-being of this young patient.

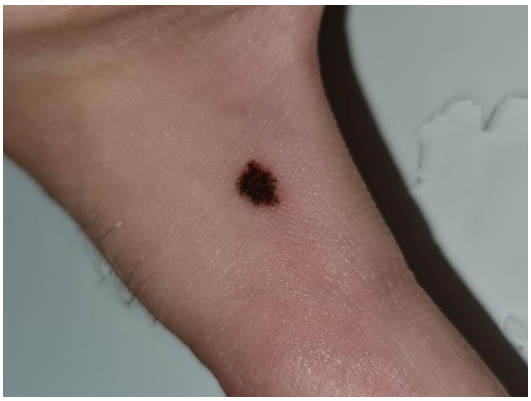


Figure 1.1 Melanoma, present in the fifth finger, medially part in a young patient.

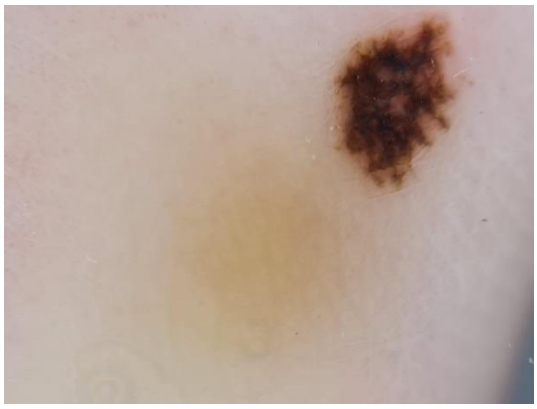


Figure 1.2 Melanoma, dermoscopy: asymmetry, atypical network, radial lines and pseudopods, blue-white veil

Case 2: Adult-Onset Melanoma: A 38-year-old female, previously unaware of the potential risks associated with melanoma, sought dermatologic consultation for a long-standing pigmented lesion on her arm (Fig 2.1) that had recently exhibited irregular changes in color and border. Utilizing dermoscopy, the lesion revealed features suggestive of melanocytic atypia (Fig 2.2), prompting prompt excision and histopathologic examination. The subsequent diagnosis of a superficial spreading melanoma with a Breslow thickness of 0.6 mm, indicative of a favorable prognosis. The successful early detection and management of this lesion averted the ominous specter of invasive disease, highlighting the pivotal role of dermoscopy in unmasking covert incipient melanomas. Continued surveillance and regular dermatologic assessments are paramount in safeguarding against potential recurrences or the emergence of new lesions in this susceptible individual.

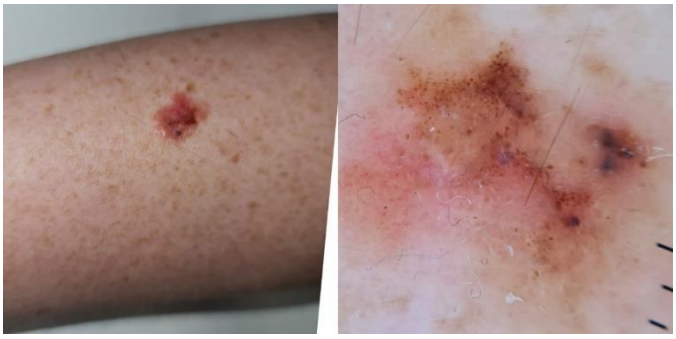


Figure 2.1 et 2.2 (2.1) Melanoma, present in the arm of an adult patient, asymmetry in colour and shape. (2.2) Dermoscopy globules and periphery brown dots, atypical vascularisation, globules, blue-white, scar-like depigmentation

Case 3: Geriatric Melanoma: A 72-year-old female, mindful of the perils of sun exposure and the potential for cutaneous malignancies, maintained a conscientious regimen of self-examination, routinely scrutinizing her extensive collection of nevi (Fig 3.1) and pigmented lesions.

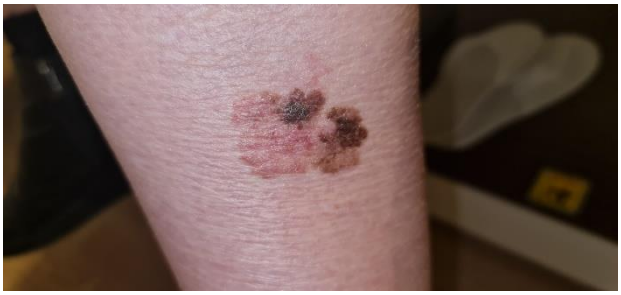


Figure 3.1 Melanoma in a geriatric patient. Asymmetry in shape, colour, more than 6 mm, present in the leg, anterior for a long time.

During her routine dermatologic visit, a previously inconspicuous lesion on her lower left leg underwent dermoscopic evaluation, revealing subtle alterations in pigment distribution and the emergence of atypical vascular structures (Fig 4.1, Fig 5.1).

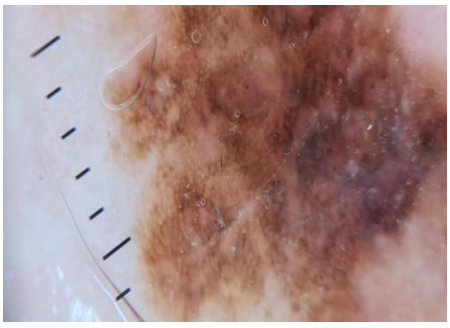


Figure 5.1 Dermoscopy of atypical melanocytic lesion (fig 3.1) in leg, atypical network, blue-white veil, periphery brown dots

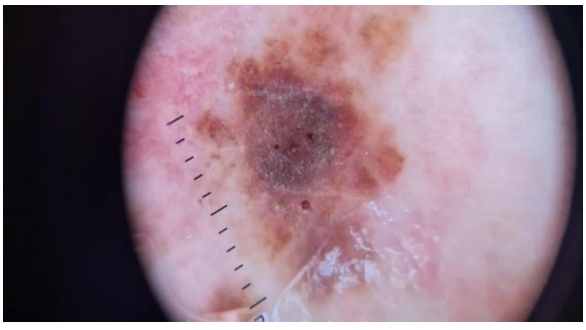


Figure 4.1 Dermoscopy of lesion (fig 3.1) atypical vascularisation, brown dots, negative and broad network.

Subsequent biopsy confirmed the diagnosis of early-stage melanoma, prompting expeditious surgical excision and sentinel lymph node evaluation. Despite the advanced age of the patient, the diligent surveillance and expeditious intervention yielded a favorable outcome, underscoring the enduring efficacy of regular dermatologic assessments in mitigating the potential morbidity of melanoma in the elderly population (Fig 6.1, Fig7.1).

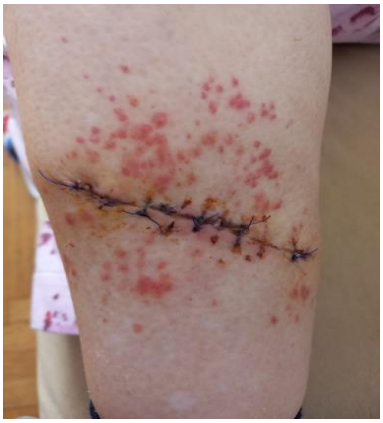


Figure 7.1 several weeks after surgery of the case in fig 3.1

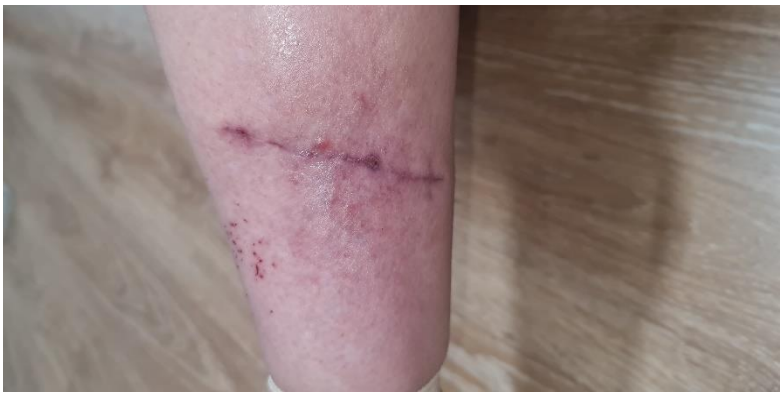


Figure 6.1 post-surgery of the case in fig 3.1.

Discussion

More than one million people are living with melanoma and one person dies from the diseases every hour. Incidence of cutaneous melanoma continues to increases each year. (1) Diagnosing at an early stage is very important. Periodic control of moles, especially in people with high predisposition (more than 100 moles, family and personal history of melanoma, unprotected sun exposure) helps to detect them in time. The cornerstone of the treatment are surgical free margin excision and histopathology/immunohistochemy (1,2). The biopsy of sentinel lymph node (SNLB) is important in staging melanoma and in clinical practice. (4,9) It is recommended in all patients with melanoma stage T1b and above, along with a subtype of T1a patients with a high-risk. (5) Fortunately, the above cases were detected at an early stage: melanoma in situ, so except the biopsy/immunohistochemy was no necessary to go further with the investigation. Follow up 6 months was recommended, because of the insidious nature of the diseases and self-check every month of the skin. According to the literature, the behaviour of melanoma does not change in different ages-group, but the incidence in younger is less compare with the adults.(2,6,7) Also, there are few report cases of melanoma in prepubertal ages. (3) These cases are the most difficult to detect because of atypical presentation of moles. (8) It is very important to emphasise that periodic control of the moles is necessary in every age, especially in the adults and the geriatric population.

Conclusion

The cases delineated above distinctly underscore the indiscriminate nature of melanoma's threat, transcending age groups and emphasizing the paramount importance of early detection through dermoscopy and sustained dermatologic surveillance. These cases also serve as poignant reminders of the success achievable through proactive engagement with healthcare providers and the enduring significance of continued follow-up in mitigating the morbidity associated with this formidable malignancy. Together, they reinforce the imperative of widespread awareness and vigilance in proactively addressing the potential morbidity of melanoma across all age demographics.

Conflict of interest: Authors declare that they have no conflict of interest.

References:

1. Susan M Swetter MD et. Al, AAD Guidelines of care for the management of primary cutaneous melanoma, Published 1 November 2018, J Am Acad Dermatol. 2019 Jan DOI: https://doi.org/10.1016/j.jaad.2018.08.055.
2. Paolo Del Fiore et al. Melanoma in Adolescents and Young Adults: Evaluation of the Characteristics, Treatment Strategies, and Prognostic Factors in a Monocentric Retrospective Study. Published online 2021 Sep 16, doi: 10.3389/fonc.2021.725523 PMCID: PMC8482997, PMID: 34604064.
3. Papas, Athanasios et al. Cutaneous Melanoma in a 9-Year-Old Girl. Case Report and Review of Literature. https://journals.lww.com/ijpd/toc/2020/21020, Indian Journal of Paediatric Dermatology 21(2):p 81-86, Apr–Jun 2020.
4. Yasuhiro Nakamura et al. The Role and Necessity of Sentinel Lymph Node Biopsy for Invasive Melanoma. Published online 2019 Oct 22:6:231. doi: 10.3389/fmed.2019.00231.
5. John T Vetto et.al .Guidance of sentinel lymph node biopsy decisions in patients with T1–T2 melanoma using gene expression profiling. Published Online:29 Jan2019 https://doi.org/10.2217/fon-2018-0912.
6. Kelly G. Paulson, MD, PhD et al. Age-Specific Incidence of Melanoma in the United States Published online 2019 Nov 13. doi: 10.1001/jamadermatol.2019.3353 PMCID: PMC6865303 PMID: 31721989, JAMA Dermatol. 2020 Jan; 156(1): 57–64.
7. Simone Ribero et al. Effect of Age on Melanoma Risk, Prognosis and Treatment Response. Acta Derm Venereol 2018 Jul 11; 98(7):624-629. doi: 10.2340/00015555-2944.
8. Paige H. Dean, BSc et al. Pediatric Melanoma: A 35-year Population-based Review Published online 2017 March 9. doi: 10.1097/GOX.0000000000001252 PMCID: PMC5404437 PMID: 28458966
9. Shannon C. Trotter et al. SC Trotter · 2013 · Cited by 222 — *J Clin Aesthet Dermatol. 2013 Sep; 6(9): 18–26*. PMCID: PMC3780800. PMID: 24062870. A *Global Review* of *Melanoma Follow-up*.
10. Aiswarya Lakshmi et al. Nice 2022 Guidelines on the management of melanoma: Update and implications. Published 19 July 2023 doi:https://doi.org/10.1016/j.bjos.2023.07.026. JPRAS, Volume 85, P401-413, October 2023.

CASE REPORT: RETROSTERNAL MULTINODULAR GOITER AND SUPERIOR VENA CAVA SYNDROME

Ergita Nelaj[1], Irida Kecaj[1], Kei Xhixhabesi[3], Denisa Çipi[1], Arben Gjata[2], Margarita Gjata[1]
[1]Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania
[2]Department of General Surgery, University Hospital Center "Mother Teresa", Tirana, Albania
[3]Faculty of Medicine, University of Medicine, Tirana, Albania

Correspondent E-mail: dr_ergi@yahoo.com

Abstract

Retrosternal enlargement of the thyroid can cause compression of several mediastinal structures. Tracheal obstruction and superior vena cava syndrome are rare complications of retrosternal goiter. We report a 60 old-year woman, complaining of hard dyspnea and with oedema of the face and the neck. She was treated for hyperthyroidism but not regurlarly. Alongside with other many examinations she had an ultrasonography of thyroid gland. The result was a giant thyroid with heterogeneous nodules, with necrotic area, in its both lobes and compressing phenomena over trachea and jugular vein. This thyroid extended to the superior mediastinum, until the tracheal bifurcation, an image confirmed by thoracic computed tomography. Thyroid needle aspiration biopsy didn't give any data for atypism and malignance. The patient had surgical intervention, total thyroidectomy. Histological examination confirmed multinodular goiter. One month after surgery, the patient had total remission of compressive signs and now, she feels well and is taking hormone replacement therapy regularly.

Keywords: retrosternal multinodular goiter; superior vena cava syndrom.

NJË RAST ME STRUMË MULTINODULARE RETROSTERNALE DHE SINDROMI I VENËS CAVA SUPERIOR.

Abstrakt

Hyrje: Struma multinodulare me shtrirje retrostrenale mund të shkaktojë kompresion të strukturave mediastinale. Obstruksioni i trakesë dhe sindromi i Venës Cava Superior janë komplikacione të rralla të kësaj strume.

Në shërbimin e Mjekësisë Interne paraqitet një grua, 60 vjeç, e cila ankonte për dispne të rëndë, cianozë, edema të fytyrës dhe qafës. Një e dhënë me rëndësi nga anamneza e të sëmurës ishte se vuante prej disa muajsh nga tiroidja për të cilën mjekohej jo rregullisht. Kjo gjë bëri që bashkë me shumë ekzaminime të tjera të bëhet dhe ekografia e gjëndrës tiroide, ku rezultoi një tiroide gjigande me formacione heterogjene, me zona nekrotike në të dy lobet e saj, dhe me fenomene komprimuese mbi trakenë dhe venat jugulare. Kjo tiroide shtrihej deri në mediastinin superior, imazh që u konfirmua dhe nga CT e toraksit. Citopunksioni i saj nuk dha të dhëna për fenomene të atipizmit qelizor e nuklear dhe as për mitoza patologjike. E sëmura iu nënshtrua ndërhyrjes kirurgjikale nga specialiste me pervojë dhe u bë tiroidektomi totale. Dhe biopsia rezultoi në favor

të strumës multinodulare. Sot e sëmura është në gjendje të mirë dhe i nënshtrohet rregullisht mjekimit me hormonoterapi zëvendësuese.

Fjalë kyçe: Struma multinodulare retrostrenale, sindromi i Venës Cava Superior.

Introduction

Retrosternal enlargement of the thyroid can cause compression of several mediastinal structures. The incidence of retrosternal goiters among patients with thyroid goiters is reported to range from approximately 5-45%(1). Tracheal obstruction and superior vena cava syndrome (SVC) are rare complications of retrosternal goiter. This syndrome usually presents with oedema and lividity of the face with enlargement of jugular and superior limbs' veins.
Malignancy is the most common cause (93 - 97%) of SVC syndrome (2). There are also rare cases reported of SVC syndrome associated with Graves' disease and multinodular goiter. Retrosternal goiter is estimated to 5 - 24 % causes of a mediastinal mass (3).

Case presentation.

In the Department of Internal Medicine, a 60 old-year woman came, complaining of hard dyspnea, retrosternal pain, cyanosis, hoarse voice. She had oedema of the face and neck with tortuous jugular vein and collateral circulation in both arms. She was having this situation for some days. By her carefully anamnesis, an important data, was the fact she had been suffering from thyroid disorders, for some months, without being cured regularly. Thyroid function tests were in the normal range. Enlarged, regional, lymph nodes were not palpable. Body temperature was 36.6°C, the heart rate was 82/min, and blood pressure was 135/85 mm Hg. The blood count was as follows: haematocrit: 49.5%, haemoglobin: 16.4g/dl, platelets: 380.000/mm^3, WBC: 11600/mm^3. Erythrocyte sedimentation rate was 12 mm in the first hour. The ECG was remarkable for sinus tachycardia, without specific ST-T changes.
Ultrasonography of thyroid gland has shown a huge thyroid with heterogeneous nodules, with necrotic area, in its both lobes, resulting in an enlargement of the gland and compressing phenomena over trachea and jugular vein. This thyroid extended to the superior mediastinum, until the tracheal bifurcation, with compression of the brachiocephalic vessels, an image confirmed by thoracic computed tomography (CT). (Fig.1) Thyroid needle aspiration biopsy didn't give any data about cell, nuclear atypism and pathologic mitosis.

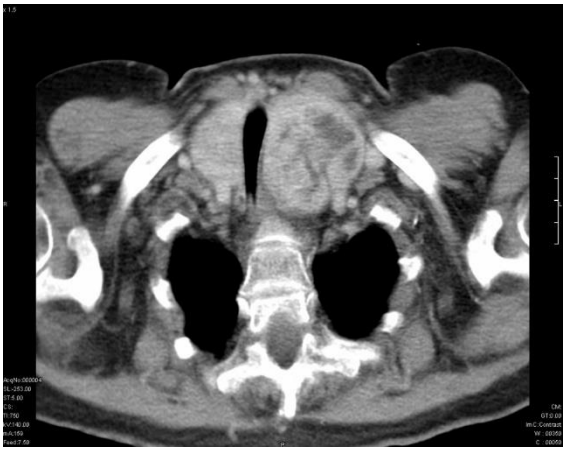


Figure. 1. CT scan of the chest. Giant retrosternal nodular thyroid gland with narrowed trachea.

The diagnosis of giant multinodular retrosternal euthyroid goiter and compression of mediastinal structures was made. The patient had surgical intervention, total thyroidectomy (Fig.2,a-b) .Histological examination confirmed nodular goiter without signs of malignancy. One month after surgery, the patient had total remission of compressive signs and now, she feels well and is taking hormone replacement therapy regularly.

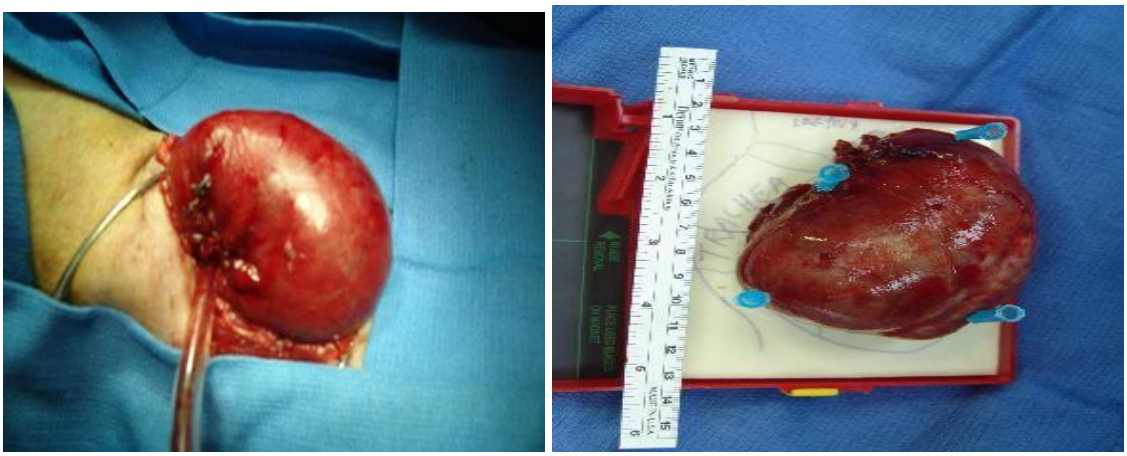


Figure 2 (a,b). Thyroid gland as surgical specimen after thyroidectomy.

Discussion

The term goiter refers to an enlargement of the thyroid. The clinical manifestations of goiter vary with the size and location of the goiter and can be potentially serious (1).
In patients with substantial enlargement of one lobe or asymmetric enlargement of both lobes, the trachea, esophagus, or blood vessels may be displaced or, less often, compressed (2). Bilateral lobar enlargement, especially if the goiter extends posterior to the trachea, may cause

either compression or concentric narrowing of the trachea or compression of the esophagus or jugular veins (3).

With some goiters, there is growth of one or both lobes through the inlet into the thoracic cavity which can result in obstruction of any of the structures in the inlet. Such goiters are called retrosternal. Retrosternal goiter was first described by Haller in 1794. Retrosternal goiter incidence varies widely depending on its definition but can be found in up to 45% of all thyroidectomies (4). Diagnosis is more common in the fifth or sixth decade of life with a female to male proportion approximately 3–4:1 (1) and have a familial component in up to 30% of cases (5).

Most retrosternal goiters are in the anterolateral mediastinum, (6) but about 10 percent are located primarily in the posterior mediastinum (7). Some patients have very low-lying thyroid glands located at the level of the thoracic inlet; in them even minimal enlargement can cause symptoms.

Etiologically, 85%–95% of retrosternal thyroid masses emerge as benign goiter (3). However, the incidence of thyroid cancer in large series of patients with retrosternal goiter has ranged from 10 to 16 percent (4,6).

Among benign retrosternal goiters, the following causes were noted in one large series (7):

- Multinodular goiter — 51 percent
- Large follicular adenoma — 44 percent
- Chronic autoimmune thyroiditis — 5 percent

The majority of patients with obstructive cervical goiters have had a visible goiter for many years. Most patients with retrosternal goiter (77 to 90 percent in two series) also have visible goiters (7,8) .

The most common complaint in patients with obstructive cervical or retrosternal goiter is exertional dyspnea, which is present in 30 to 60 percent of cases (5,7,9) . This symptom usually occurs when the tracheal diameter is under 8 mm (10). In some patients with substernal goiter, dyspnea is primarily positional or nocturnal, and it occurs primarily during maneuvers that force the thyroid into the thoracic inlet such as reaching and bending (11). When tracheal compression becomes severe (luminal diameter less than 5 mm), stridor or wheezing occurs at rest (10,11). This upper airway wheezing must be distinguished from asthma. An upper respiratory illness may exacerbate upper airway obstruction.

Obstructive goiter rarely, can induced jugular vein compression or thrombosis, cerebrovascular steal syndromes, or even the superior vena cava syndrome (12,13). However, retrosternal goiter as a cause is extremely rare. The incidence of retrosternal goiter causing SVC syndrome is 3.2% (14) and may be asymptomatic for a long period due to the slow but steady growth of the gland on account of venous collateral development (15). Compression of the superior vena cava by a mediastinal malignancy is the most common cause of SVC syndrome (16).

Substernal goiters are often seen on chest x-ray as a mass that causes tracheal narrowing or deviation or as superior mediastinal widening. However, the extent of the goiter and its effect upon surrounding structures can be assessed better by computed tomography (CT) or magnetic resonance imaging (MRI) (5,12,17). Thyroid ultrasonography, although more accurate than CT for defining thyroid anatomy in the anterior neck, is not satisfactory for imaging of posterior neck structures or the substernal region.

Surgery is the treatment of choice for any goiter causing obstructive symptoms, and for significant retrosternal goiters whether or not obstructive symptoms are present (7,12,15).

The majority of obstructive and retrosternal goiters can be excised through a standard collar incision. However, to remove a very large retrosternal goiter, or invasive cancer, partial or complete sternotomy or even thoracotomy may be required (12).
Radioiodine (131-I) may be useful as nonsurgical treatment for obstructive or retrosternal goiter. Despite the apparent success of radioiodine, surgery is still the treatment of choice because of concern that radiation thyroiditis might result in worsening of airway obstruction and the possibility of carcinoma if the goiter is mostly substernal (17). Radioiodine may be useful in patients who refuse surgery or are poor surgical candidates, particularly if the retrosternal or obstructive goitrous tissue is functional on thyroid radionuclide imaging.

As conclusion, based on the presented case, in patients with SVC syndrome should have a careful thyroid exam and early diagnosis and proper treatment of SVC syndrome due to thyroid pathologies may prove to be lifesaving.

Conflict of interest: The authors have no conflicts of interest to declare.

References

1. Doulaptsi M, Karatzanis A, Prokopakis E, Velegrakis S, Loutsidi A, Trachalaki A et al, 2019 Substernal goiter: treatment and challenges. Twenty-two years of experience in diagnosis and management of substernal goiters. Auris Nasus Larynx 46:246–251.

2. Shah RP, Bolaji O, Duhan S, Ariaga AC, Keisham B, Paul T, Aljaroudi W, Alraies MC. Superior Vena Cava Syndrome: An Umbrella Review. Cureus. 2023 Jul 20;15(7):e42227. doi: 10.7759/cureus.42227. PMID: 37605686; PMCID: PMC10439982.

3. Aghajanzadeh M, Asgary MR, Mohammadi F, Darvishi H, Safarpour Y. An investigation into symptoms, diagnosis, treatment, and treatment complications in patients with retrosternal goiter. J Family Med Prim Care. 2018 Jan-Feb;7(1):224-229. doi: 10.4103/jfmpc.jfmpc_286_17. PMID: 29915764.

4. Castro LS, Timóteo J, Aparício D, et al. Features of Superior Vena Cava Syndrome Secondary to Noninvasive Thyroid Tumor: A Case Report. World J Endoc Surg 2022;14(3):84–86.

5. Cullinane C, Evoy D, McDermott E, Prichard R. The surgical management of retrosternal goiter; an ongoing controversy. World J Surg Surg Res 2021;4:1328.

6. Uncu, Hakan MD*; Arbal, Dikmen MD†ı. Multinodular Goiter Causing Tracheal Compression and Superior Vena Cava Syndrome: A Case Report. The Endocrinologist 18(4):p 167-169, July 2008. | DOI: 10.1097/TEN.0b013e3181815a6e.

7. Newman, E, Shaha, AR. Substernal goiter. J Surgical Oncology 2006; 60:207.

8. Bukhari H, Ayad M, Rosenthal A, Block M, Cortelli M. Superior vena cava syndrome secondary to thyroid cancer. J Surg Case Rep 2011;7.

9. Evrim Cakir. Superior vena cava syndrome due to enlarged thyroid gland. Presented at Society for Endocrinology BES 2013, Denmark, Endocrine Abstracts (2013) 32 P1063.

10. Khayat S, Al-Juaid A, Khorchid A, Othman M, Othman B, Al-zahrani A. Retrosternal goiter with posterior mediastinal extension surgery in a patient with superior vena cava obstruction through a classic neck incision; Case report. WebmedCentral SURGERY 2015;6(5):WMC004890.

11. Samokhvalova, A., N. Loberantb, and N. Makhoula, Posterior mediastinal goiters: Report of two cases and literature review. Respiratory Medicine Case Reports, 2012. 5: p. 65-8.

12. Knobel M. An overview of retrosternal goiter. J Endocrinol Invest 2021;44:679–691.

13. Gorniak A, Carlson-Dexter P, Ochoa J, et al Substernal multinodular goiter resulting in superior vena cava syndrome and tracheal compression BMJ Case Reports CP 2023;16:e252827.

14. Idrees S, Mayilvaganan S. The Imminent Sign of SVC Syndrome Secondary to Retrosternal Goiter. J Endocr Surg. 2021 Dec;21(4):118 122. https://doi.org/10.16956/jes.2021.21.4.118.

15. Giulea C, Enciu O, Nadragea M, Badiu C, Miron A. Pemberton's sign and intense facial edema in superior vena cava syndrome due to retrosternal goiter. Acta Endocrinol (Bucur) 2016; 12:227–229.

16. Kayla Blanchard, Clio Musurakis, Ankita Ojha, Charles P Barsano, Andriy Havrylyan, SAT486 A Case of Superior Vena Cava Syndrome Caused by Untreated Multinodular Goiter, Journal of the Endocrine Society, Volume 7, Issue Supplement_1, October-November 2023, bvad114.1959, https://doi.org/10.1210/jendso/bvad114.1959.

17. Chakravarty S, Nagarkar NM, Ghosh A, Mehta R. Retrosternal Thyroid with Mediastinal Extension: Surgical Approach and Management. Indian J Otolaryngol Head Neck Surg. 2023 Jun;75(2):332-337. doi: 10.1007/s12070-022-03231-w. Epub 2022 Nov 6. PMID: 37275118; PMCID: PMC10235387.

THE IMPORTANCE OF SERUM PROTEIN ELECTROPHORESIS: A CASE REPORT

Hamide Shllaku-Sefa[1], Ervin Marku[2], Manjola Qordja[1], Gentian Kasmi[1], Ndok Marku[1]
[1]Laboratory Department, Catholic Hospital "Our Lady of Good Counsel", Tirana, Albania
[2]Department of Pre-Clinical Subjects, Faculty of Technical Medical Sciences, University of Medicine, Tirana, Albania

Correspondent E-email: sefadea@gmail.com

Abstract

Background: Serum protein electrophoresis is a test that measures specific proteins in the blood. Electrophoresis separates proteins based on their physical properties. The principal clinical use of an serum protein electrophoresis is to determine which of the globulin proteins is elevated and to differentiate monoclonal from polyclonal gammopathies. This differentiation is vitally important because monoclonal gammopathies, which are indicated by evidence of a monoclonal M band on the serum protein electrophoresis, indicate malignant or premalignant conditions.

Methods: During our daily routine in the laboratory, we casually found an elevated total protein. In this case, we decided to perform a serum protein electrophoresis. We used the cellulose acetate electrophoresis system ADALYA IFE.
Results: K.Z., female, 57 years old, come to the laboratory for a general checkup. Blood sugar 121 mg/dl, urea 40 mg/dl, creatinine 0.89 mg/dl, alkaline phosphatase 90 UI/L, ALT 53 UI/L, AST 33 UI/L, total bilirubin 0.4 mg/dl, GGT 40 UI/L, total protein 9.8 g/dl, albumin 3.8 g/dl, sodium 138 mmol/l, potassium 4.1 mmol/l, chloride 99 mmol/l, normal prothrombin time, erythrocyte sedimentation rate 94 mm/h, and a normal complete blood count, except platelets 127 x 10*3/µL. We performed serum protein electrophoresis, and we found a monoclonal gammopathy (34.7 % gamma globulin). After that, we did immunofixation: IgA 31 mg/dL, IgM 26 mg/dL, IgG 3518 mg/dL, kappa 0.170 g/L, lambda 10.186 g/L, and kappa/lambda ratio 0.02. Considering the importance of these results, we refer the patient to a hematologist for further investigation, diagnosis, treatment, and follow up.
Conclusions: Serum protein electrophoresis is an easy, inexpensive test that should always be performed in patients with elevated levels of total protein.

Keywords: protein, electrophoresis, monoclonal, gamma.

RËNDËSIA E ELEKTROFOREZËS SË PROTEINAVE: STUDIM RASTI

Abstrakt

Hyrje: Elektroforeza e proteinave është një test që mat proteinat specifike në gjak. Elektroforeza ndan proteinat në bazë të vetive të tyre fizike. Përdorimi kryesor klinik i një elektroforeze të proteinave është të përcaktojë se cila nga fraksionet e globulinave është e rritur dhe të diferencojë gamopatitë monoklonale nga ato poliklonale. Ky diferencim është me rëndësi jetike, sepse gamopatitë monoklonale, të cilat tregohen nga evidenca e një brezi monoklonal në elektroforezë, tregojnë gjendje malinje ose paramalinje.

Metodat: Gjatë rutinës sonë të përditshme në laborator, rastësisht gjetëm një proteinë totale të rritur. Në këtë rast vendosëm të kryejmë një elektroforezë të proteinave. Ne përdorëm sistemin elektroforezë të acetatit të celulozës ADALYA IFE.

Rezultatet: K.Z, femër, 57 vjeç, vjen në laborator për një kontroll të përgjithshëm. Glicemi 121 mg/dl, urea 40 mg/dl, kreatinina 0,89 mg/dl, fosfataza alkaline 90 UI/L, ALT 53 UI/L, AST 33 UI/L, bilirubina totale 0,4 mg/dl, GGT 40 UIL, proteina totale 9,8 g/dl, albumina 3,8 g/dl, natriumi 138 mmol/l, kalium 4,1 mmol/l, klor 99 mmol/l, koha e protrombinës normale, eritrosedimenti 94 mm/h dhe gjaku komplet normal, përveç trombocitet 127 x 10*3/µL.
Në elektroforezën e kryer kemi gjetur një gamopati monoklonale (34,7 % gama globulinë). Pas kësaj kemi bërë imunofiksim: IgA 31 mg/dL, IgM 26 mg/dL, IgG 3518 mg/dL, kappa 0,170 g/L, lambda 10,186 g/L, dhe raporti kappa/lambda 0,02. Duke marrë parasysh rëndësinë e këtyre rezultateve, ne e referuam pacientin tek një mjek hematolog për ekzaminime të mëtejshme, diagnostikim, trajtim dhe ndjekje.
Përfundime: Elektroforeza e proteinave është një test i lehtë dhe i lirë që duhet të kryhet gjithmonë te pacientët me nivele të larta të proteinës totale.

Fjalë kyçe: proteina, elektroforezë, monoklonale, gama.

Introduction

Serum protein electrophoresis (SPEP) is a method of separating proteins based on their physical properties. Serum is placed on a specific medium, and a charge is applied. The net charge (positive or negative) and the size and shape of the protein are commonly used in differentiating various serum proteins. The proteins are stained, and their densities are calculated electronically to provide graphical data on the absolute and relative amounts of the various proteins. Further separation of protein subtypes is achieved by staining with an immunologically active agent, which results in immunofluorescence and immunofixation (1). There are two types of proteins present in the serum: albumin, and the globulin proteins. Albumin is the biggest component of serum proteins and represents the largest peak that lies closest to the positive electrode. Globulins are divided into five categories: alpha-1, alpha-2, beta-1, beta-2, and the gamma fraction, which is closest to the negative electrode (2).
Serum protein electrophoresis is generally considered in any patient with an elevated total protein, especially those with elevated globulin level relative to albumin, or any signs and symptoms suggestive of an underlying plasma cell disorder (3,4) It is extremely important that during the interpretation of serum protein lectrophoresis, to differentiate monoclonal from polyclonal gammopathies. Monoclonal gammopathies are associated with a clonal process that is malignant or potentially malignant.
Diseases that produce an increase in the gamma-globulin level include Hodgkin’s disease, malignant lymphoma, chronic lymphocytic leukemia, granulomatous diseases, connective tissue diseases, liver diseases, multiple myeloma, Waldenström’s macroglobulinemia, and amyloidosis (1,5).
On the other hand, polyclonal gammopathies may be caused by any reactive or inflammatory process, and they are usually associated with nonmalignant conditions. The most common causes of polyclonal gammopathies are infections. These can include parasitic infections, fungal infections, bacterial infections, spirochete infections, and viral infections (6,7).

We aim to underline the importance of protein electrophoresis in outpatients with increased levels of total protein.

Materials and methods

We collected blood samples through venipuncture using BD Vacutainer k3EDTA 5.4 mg, 3 mL tubes for complete blood count (CBC) and measured on ADVIA 2120i, Haematology System, and for erythrocyte sedimentation rate measured in Diesse Cube 30Touch. We used BD Vacutainer 9NC 0.109M, Buff.Na3 Citrate 2.7 ml tubes to evaluate prothrombin time measured on Sysmex Ca-600 series.

For the measurement of the other biochemical tests, we collected the blood with a BD Vacutainer SST II Advance 3.5 ml tube, and we measured it with Dimension EXL 200.

We used the cellulose acetate electrophoresis system (ADALYA IFE).

Case presentation.

We present here a 57 year old female patient who comes to our laboratory on the recommendation of the general practitioner to perform a checkup. The laboratory results are as follows: glicemia 121 mg/dl, urea 40 mg/dl, creatinine 0.89 mg/dl, alkaline phosphatase 90 UI/L, ALT 53 UI/L, AST 33 UI/L, total bilirubin 0.4 mg/dl, GGT 40 UI/L, total protein 9.8 g/dl, albumin 3.8 g/dl, sodium 138 mmol/l, potassium 4.1 mmol/l, chloride 99 mmol/l, normal prothrombin time, erythrocyte sedimentation rate 94 mm/h, and a normal complete blood count, except platelets 127 x 10*3/µL. Faced with this situation, we decided to perform a serum protein electrophoresis. At the end of the day, we found a monoclonal gammopathy (34.7 % gamma globulin). After that, we did immunofixation: IgA 31 mg/dL, IgM 26 mg/dL, IgG 3518 mg/dL, kappa 0.170 g/L, lambda 10.186 g/L, and kappa/lambda ratio 0.02. Due to an administrative inconvenience, we were unable to communicate with the patient or her general practitioner, but fortunately she came a few weeks later. Once again, after the results were obtained, the general practitioner did not ask for a protein electrophoresis. In the laboratory examinations done a few weeks later, the results are as follows: total protein 12.5 g/dl, urea 77 mg/dl, creatinine 4.02 mg/dl, erythrocyte sedimentation rate 140 mm/h, red blood cells 2.71 x $10^{6/}$µL, hemoglobin 8.8 g/dL, hematocrit 24.4%, platelets 110 x 10^{3}/µL.

On the skeletal radiography, the radiologist saw a Th12 compression fracture and osteopenia. Considering the importance of these results we refer the patient to a hematologist - oncologist for further investigation, diagnosis, treatment, and follow-up, and she decided to go for further examinations in a specialized center abroad.

Discussion

Based on the data we have from our case: a M-protein in serum 30 g/l; abnormal kidney function with a serum creatinine 4.02 mg/dL and a calculated creatinine clearance (2021CKD-Epi) 12 ml/min; anemia, with a hemoglobin 8.8 g/dL; and bone lesions, and the diagnostic criteria of monoclonal gammopathies, the most likely diagnosis is multiple myeloma (8).

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common hematological malignancy, with an estimated incidence in Europe of 4.5-6.0/100 000/y (9).

According to the guidelines developed by the European Hematology Association (EHA) and the European Society for Medical Oncology (ESMO), there are several tests obligatory for the diagnosis of multiple myeloma (10).

These tests are divided into blood tests that include blood count and blood smear, serum electrophoresis and immunofixation, serum-free light chain, serum immunoglobulin levels, renal and liver function tests, calcium, lactate dehydrogenase, albumin, and β2-microglobulin. In urine: urine sample from a 24 hour urine collection to check for proteinuria and light-chain proteinuria, urine electrophoresis, and immunofixation. In bone marrow: bone marrow cytology and biopsy to confirm plasmacytosis and monoclonality, next-generation flow cytometry or next-generation sequencing to detect clonal plasma cells, cytogenetics: karyotype and FISH for detection of del 17p, t (4;14), t (14;16), ampl 1q/gain 1q, t (11;14). We are aware that we are not a specialized center for onco-hematological pathologies, however, the results obtained from our laboratory made it possible to understand that the patient had a serious health problem for which she would undergo specific examinations.

Conclusion

Serum protein electrophoresis is an easy, inexpensive test, and clinicians should always ask for it in cases where they find an increased level of total protein in their patients.

References

1. O'Connell TX, Horita TJ, Kasravi B. Understanding and interpreting serum protein electrophoresis. Am Fam Physician. 2005 Jan 1;71(1):105-12. PMID: 15663032.
2. Dupree, Shandi. *Electrophoresis (Methods in Biochemistry)*. 1st edition. New Delhi, India: World Technologies, Publishing; 2012 Jan 1.
3. Munshi NC, Longo DL, Anderson KC. *Plasma cell disorders: Harrison's Principles of Internal Medicine*. 18th ed. The McGraw-Hill Companies; 2005.
4. Hoffman R, et al. Hematology: basic principles and practice. 3d ed. New York: Churchill Livingstone, 2000:369–70,1403,2505–9.
5. Kyle RA. The monoclonal gammopathies. *Clin Chem.* 1994;40(11 pt 2):2154-61.
6. Dispenzieri A, Gertz MA, Therneau TM, Kyle RA. Retrospective cohort study of 148 patients with polyclonal gammopathy. *Mayo Clin Proc.* 2001; 76:476-87.
7. Wallach JB. Interpretation of diagnostic tests. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:78–83.
8. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Aug;97(8):1086-1107. Doi: 10.1002/ajh.26590.
9. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma - an IMWG research project. *Blood Cancer J*. 2018; 8:123.
10. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Hemasphere. 2021 Feb 3;5(2): e528. Doi: 10.1097/HS9.0000000000000528.

POST-PARTUM CARDIOMYOPATHY AND STROKE. CASE REPORT

Malbora Xhelili[1], Ilirjana Zekja[2] , Eliverta Konda-Majko[3], Arben Rroji[4], Jera Kruja[1,2],
[1]UHC "Mother Teresa" , University of Medicine, Faculty of Medicine, Neurology Service, Tirana, Albania
[2]UHC "Mother Teresa", Neurology Service, Tirana, Albania
[3]UHC "Mother Teresa", Neurology Service, Cardiologist
[4]UHC "Mother Teresa", Radiology Service, Albania

Correspondent E-email: neuroalbania@live.com

Abstract

Background. Postpartum cardiomyopathy, also known as peripartum cardiomyopathy, is one of the rare causes of stroke in young females. Postpartum cardiomyopathy is defined as new- onset heart failure between the last month of pregnancy and 5 months post-delivery with no determinable cause. Risk factors include multiparity, advanced maternal age, multiple pregnancies, pre-eclampsia, chronic hypertension, smoking, alcoholism, malnutrition, and long-term tocolysis.
Methods: We describe the case of a 34-year-old patient who was admitted for shortness of breath, rapidly worsening into asthma cardiae three months after the delivery of her second baby. One week later, she presented in the neurology emergency room with an acute onset of left hemiparesis and difficulty speaking.
Results: The Magnetic Resonance Imaging showed a wedge-shaped hypodensity involving the gray and white matter of the right anterior temporal and parietal lobe, features suggestive of hemodynamic right-sided acute ischemic stroke.
Conclusion: This case highlights the importance of multidisciplinary team collaboration in the clinical approach for further evaluation and proper treatment of postpartum cardiomyopathy patients complicated by stroke.

Keywords: peripartum cardiomyopathy, female, stroke, interprofessional team members.

KARDIOMIOPATIA POST-PARTUM DHE INSULTI CEREBRAL

Abstrakt

Hyrje. Kardiomiopatia pas lindjes, e njohur gjithashtu si kardiomiopatia peripartum është një nga shkaqet e rralla të insultit tek femrat e reja. Kardiomiopatia pas lindjes përkufizohet si insuficiencë kardiake me prezantim për herë të parë midis muajit të fundit të shtatzënisë dhe 5 muaj pas lindjes, pa ndonjë shkak të përcaktuar. Faktorët e rrezikut përfshijnë multiparitetin, moshën e përparuar të nënës, shtatzënitë e shumëfishta, pre-eklampsinë, hipertensionin kronik, duhanin, alkoolizmin, kequshqyerjen dhe tokolizën afatgjatë.
Metodat: Përshkruajmë rastin e një pacienteje 34 vjeçare, e cila u shtrua për dispne që përkeqësohej me shpejtësi në astmë kardiake, tre muaj pas lindjes së foshnjës së dytë. Një javë

më vonë ajo u paraqit në Urgjencën e Neurologjisë me fillim akut të hemiparezës së majtë dhe vështirësi në të folur.
Rezultatet: Rezonanca magnetike tregoi një hipodensitet që përfshin lëndën gri dhe të bardhë të lobit anterior të djathtë dhe parietal, tipare që sugjerojnë për lezione akute ishemike hemodinamike në anën e djathtë.
Konkluzionet: Ky rast nxjerr në pah rëndësinë e bashkëpunimit në ekip multidisiplinar, në përqasjen klinike, për vlerësimin e mëtejshëm dhe trajtimin e duhur të pacientëve me kardiomiopati pas lindjes, të komplikuar me insult.

Fialë kyçe: kardiomiopati peripartum, femra, insulti, anëtarë të ekipit interprofesional

Introduction

Postpartum cardiomyopathy, also known as peripartum cardiomyopathy (PPCM), is defined as new-onset heart failure between the last month of pregnancy and 5 months post-delivery with no determinable cause (1). Postpartum cardiomyopathy is a rare cause of heart failure and stroke in young females. Heart failure in the peripartum period was first described in 1849. The overall incidence of PPCM ranges from 1 in 1300 to 1 in 15,000 pregnancies. However, the incidence fluctuates globally and is higher in developing countries. The 2010 European Society of Cardiology (ESC) (2) Working Group defined PPCM as an idiopathic cardiomyopathy with the following characteristics:
1. The development of heart failure (HF) towards the end of pregnancy or within five months following delivery.
2. The absence of an identifiable cause of HF.
3. Left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of less than 45 percent. The LV may or may not be dilated.
The exact mechanism of disease is unknown; however, different hypotheses have been described regarding its etiology, comprising: viral myocarditis, nutritional deficiencies, autoimmunity, hemodynamic stresses, vascular dysfunction, hormonal insults, and underlying genetics. Altered prolactin processing, and elevated soluble Fms-like tyrosine kinase 1 (Flt 1) (3) have also been associated with the pathogenesis of PPCM. Prolactin is a hormone released from the pituitary gland late in pregnancy and after delivery that stimulates breast milk production. But prolactin may have adverse effects on the heart muscle by limiting its blood supply and causing cell death. During pregnancy, increased oxidative stress leads to cleavage of prolactin by cathepsin D into an abnormal 16-kDa protein. This protein damages the heart and blood vessels. Soluble Flt 1 is secreted by the placenta and inhibits vascular endothelial growth factor signaling, which leads to angiogenic imbalance and endothelial dysfunction (4). Relaxin-2, a hormone produced by the ovaries, breast, and placenta, has a potential beneficial effect in PPCM. It increases cardiac output and decreases vascular resistance. However, postpartum cardiomyopathy is a diagnosis of exclusion, despite many attempts to establish the exact etiology and pathophysiology (5).
Risk factors are increased parity, increased maternal age, smoking, preclampsia, eclampsia, chronic hypertension, alcoholism, use of tocolytics, and malnutrition (6).
Patients usually present with shortness of breath, orthopnea, cough, hemoptysis, paroxysmal nocturnal dyspnea, and ankle edema. Tachycardia, elevated jugular venous pressure, the third heart sound (S3) (7), and a displaced apex beat are common. About 6 % of patients (8) of PPCM

present with thromboembolic complications such as deep vein thrombosis (9), pulmonary thromboembolism, stroke (10), acute limb ischemia (11), etc.
Here, we report a rare case of a young female with peripartum cardiomyopathy complicated by stroke.

Case report

A 34- year-old female ex-smoker patient, three months after giving birth to her second child, presented in the Emergency Room after developing a 40 minute episode with slurring of speech, difficulty moving her left half of the body, and left hemihypoesthesia. She was hospitalized a week prior in the Pulmonary Department with severe fatigue, palpitations, a non-productive cough, low blood pressure (90/50mmHg), and progressive dyspnea with an oxygen saturation of 80%. There was no history of fever, chest pain, or hemoptysis. The family history was positive for premature coronary artery disease and premature death. She reported that her mother and her grandmother died around the age of 50 from cardiac disease.
On examination, the patient had a temperature of 36.6°C, heart rate of 123 beats per minute, blood pressure was 90/70 mmHg, respiratory rate of 22 breaths per minute and oxygen saturation of 93%. There was no peripheral edema. The chest examination and other systems were unremarkable.
On investigation, laboratoric tests were all normal,except of a high NTproBNP (4973.30). (Details are shown in Table 1.)

Table 1. Laboratory parameters on admission.

Parameters	On admission	Reference Range (adults)
Hematocrit (%)	48,4	42-52
Hemoglobin (g/dl)	15,0	13-17
White-cell count (per mm3)	9,5	4-10,5
Differential count (%)		
Neutrophils	52,9	40-72
Eosinophils	2,2	<5
Lymphocytes	35,7	25-45
Monocytes	8,99	3-9
Mean corpuscular volume (fL)	85,8	80-100
Prothrombin time (sec)	12,5	11-14
Creatinine (mg/dl)	0,79	0,72-1,25
Sodium (mmol/liter)	138	136-145
Potassium (mmol/liter)	4,2	3,5-5,1
Random blood sugar (mg/dl)	86	74-100
Urea (mg/dl)	32,7	19,1-44,1
Total bilirubin (mg/dl)	0,35	0,3-1,2
CRP (mg/dl)	0,13	< 0,5
Alanine transaminase (IU/L)	45	< 55
Aspartate transaminase (IU/L)	30	5-34

CK(IU/L)	78	30-200
CK-MB Imuno (ng/ml)	2,8	< 5,2
Troponine I (ng/ml)	0,001	< 0,034
NTproBNP	4973.30	< 125

On neurological examination, the patient had left-sided upper motor neuron type facial nerve palsy, muscle strengths in the left upper and lower limbs were 4/5 and 5/5, respectively, on the Medical Research Council (MRC) scale, and there was an ipsilateral Babinski sign.

A computed tomography scan of the head and a computed tomography angiography (CTA) of the supraaortic arteries were performed immediately and were both normal. The MRI showed a wedge- shaped hypodensity involving the gray and white matter of the right anterior temporal and parietal lobe, features suggestive of hemodynamic right sided acute ischemic stroke. [Figure 1]. An electrocardiogram showed sinus tachycardia.

Transthoracic echocardiography (TTE) showed global hypokinesia of the left ventricular wall with an LVEF of 25%, moderate mitral regurgitation, and left ventricular dilatation.

A diagnosis of right sided ischemic stroke (hemodynamic) with peripartum cardiomyopathy was formulated. The patient was treated with Aspirin 100 mg daily, Furosemide 20 mg twice a day, Spironolactone 25 mg daily, Metoprolol 12,5 mg daily, and prophylactic low molecular weight heparin (UFH) 4000 units subcutaneously once a day. She was initiated Entresto (Sacubitil/Valsartan) 50 mg daily,under rigorous surveillance of the hemodynamic parameters. At the time of discharge, her speaking improved significally and there were no motor deficits. The patient was counseled about avoiding subsequent pregnancies. Anticoagulation was started two weeks following the ischemic stroke to avoid the risk of bleeding, as the infarct involved more than one-third of the right middle cerebral artery region. Anticoagulation in PPMC is administered when LVEF is < 30%.

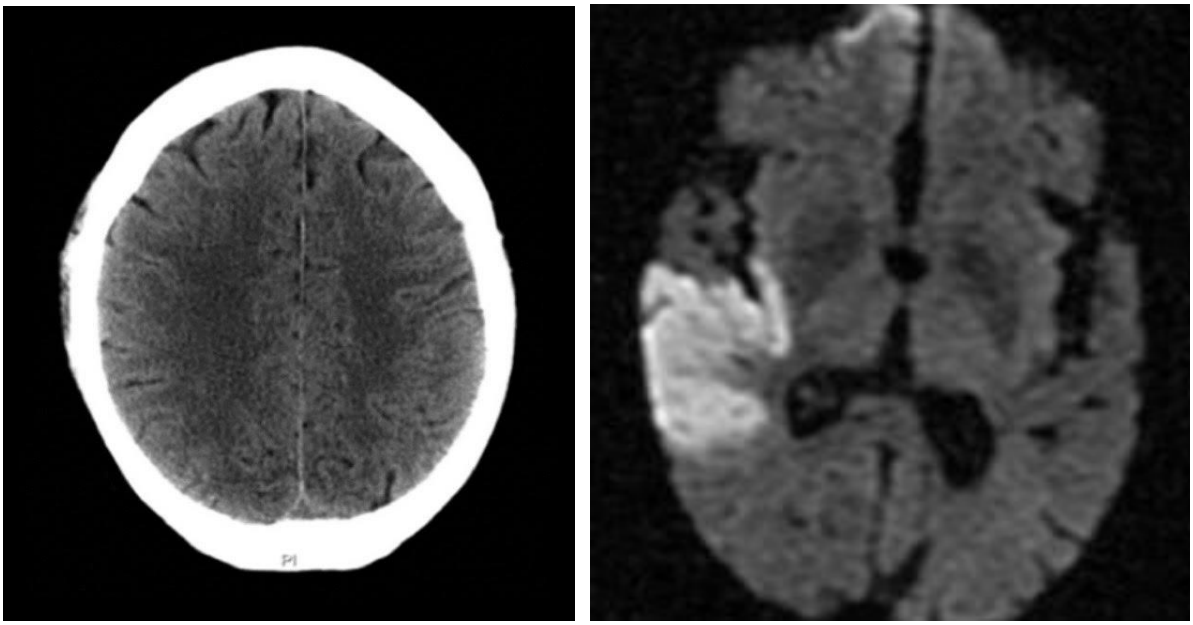


Figure 1. Normal CT scan and Magnetic Resonance (MRI) showing right sided acute ischemic stroke.

Discussion and Recommendations

Peripartum cardiomyopathy is a rare disease of unknown cause that strikes women and is associated with a high mortality rate. Strokes in young adults are uncommon, and the diagnosis is challenging and requires vigilance.
In our patient, the etiology was secondary to hypokinesia of the left ventricle (EF=25%) due to peripartum cardiomyopathy. Maternal age > 30 years,smoking, and family history are the risk factors for PPCM in this case. Other conventional risk factors for PPCM, such as multiple pregnancies, the use of tocolytics, and preeclampsia, or eclampsia were not present in our patient. The management of PPCM complicated by stroke requires a multidisciplinary approach that involves a cardiologist, neurologist, obstetrician, psychologist and physiotherapist.
Ongoing studies are needed to help researchers better understand the cause of PPCM and develop new treatments. Health care professionals have tried treatments that alter the immune system, such as intravenous γ-globulin, but they're not proven. Researchers have also focused on the role of prolactin in PPCM, as it may have adverse effects on the heart muscle by limiting its blood supply and causing cell death. Bromocryptine is a medication that inhibits the pituitary secretion of prolactin. Early studies suggest it helps treat PPCM, but more research is needed.

Conclusion

PPCM is a rare cause of stroke in postpartum patients, and an interprofessional approach is essential in the diagnosis and management. One should consider PPCM as a differential diagnosis in any patient presenting with shortness of breath and cough during puerperium. Early diagnosis and therapy prevents further complications.

Conflict of interest. None declared.

References

1. Pradhan RR, Yadav AK, Yadav S and Gupta PK. Case Report: Peripartum cardiomyopathy in a young female complicated by cardioembolic stroke F1000Research 2019, 8:2135.
2. Varona JF, Guerra JM, Bermejo F, et al.: Causes of ischemic stroke in young adults, and evolution of the etiological diagnosis over the long term. Eur Neurol. 2007; 57(4): 212–8.
3. Bhattacharyya A, Basra SS, Sen P, et al.: Peripartum cardiomyopathy: a review. Tex Heart Inst J. 2012; 39(1): 8–16.
4. Smajlović D: Strokes in young adults: epidemiology and prevention. Vasc Health Risk Manag. 2015; 11: 157–64.
5. Howie PW: Anticoagulants in pregnancy. Clin Obstet Gynaecol. 1986; 13(2): 349–63.
6. Kumbham P, Sharma B, Patel A, et al.: POSTPARTUM CARDIOMYOPATHY WITH CARDIOEMBOLIC STROKE (P3.298). Neurology. 2017; 88(16 Supplement): P3.298.
7. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al.: Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology.

8. Elkayam U.Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. J Am Coll Cardiol 2011; 58:659-70. doi:10.1016/j.jacc.2011.03.047 pmid:21816300.
9. Barasa A, Rosengren A, Sandström TZ, Ladfors L, Schaufelberger M
10. Heart failure in late pregnancy and postpartum: incidence and long-term mortality in Sweden from 1997 to 2010. J Card Fail2017.
11. Warner JJ, Harrington RA, Sacco RL, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. *Stroke.* 2019;50(12):3331–3332. doi: 10.1161/STROKEAHA.119.027708.
12. Dyken ME, Biller J. Peripartum cardiomyopathy and stroke. *Cerebrovasc Dis.* 1994;4(4):325–328. doi: 10.1159/000108502.

HYPERFUNCTIONING NODULAR GOITER ASSOCIATED WITH GRAVES' ORBITOPATHY AND PAPILLARY CARCINOMA: A CASE SERIES AND REVIEW OF LITERATURE

Marjeta Kermaj, Dorina Ylli, Violeta Hoxha, Agron Ylli
Department of Endocrinology, U.H.C. "Mother Teresa," Tirana, Albania.

Corespondent E-mail: marjetak17@gmail.com.

Abstract

This article presents a case series of three patients diagnosed with hyperfunctioning nodular goiter associated with Graves' orbitopathy, one of whom was also found to have papillary thyroid carcinoma. The rarity of coexisting Graves' orbitopathy, and toxic nodular goiter is discussed, highlighting the emergence of Graves' disease in such cases.

Introduction: The coexistence of Graves' orbitopathy and toxic nodular goiter is a rare occurrence, representing the emergence of Graves' disease.While hyperthyroidism is believed to protect against thyroid cancer, recent studies suggest that the incidence of malignancy in toxic nodular goiter is not as low as previously thought.

Methods: Detailed clinical, laboratory, and radiological findings of the three cases are provided, with diagnostic confirmation achieved through 99m Tc thyroid scintigraphy, confirming toxic nodular goiter as the cause of hyperthyroidism. Biopsy post-total thyroidectomy revealed papillary thyroid carcinoma in one case. Treatment options, including antithyroid drugs, synthetic glucocorticoids, and surgical interventions, are discussed.

Results: All three cases presented with hyperthyroidism and Graves' orbitopathy, with two undergoing total thyroidectomies, uncovering papillary thyroid carcinoma within toxic adenomas. The third patient opted for methimazole treatment. The successful management of Graves' orbitopathy with high-dose pulse glucocorticoids is discussed, along with the challenges of managing toxic nodular goiter and active Graves' orbitopathy concurrently.

Conclusion: Toxic nodular goiter accompanied by infiltrative ophthalmopathy represents the emergence of Graves' disease, confirmed by the presence of Antibodies to the thyrotropin receptor. Surgical intervention is considered a crucial therapeutic modality, especially in cases where toxic nodular goiter coexists with Graves' orbitopathy. The article underscores the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in such complex cases.

Keywords: Hyperfunctioning nodular goiter, Graves'orbitopathy, papillary thyroid carcinoma, thyrotropin-stimulating hormone receptor antibodies.

STRUMA NODULARE HIPERFUNKSIONANTE E SHOQËRUAR ME GRAVES'ORBITOPATI DHE KARCINOMË PAPILARE: NJË SERI RASTESH KLINIKE DHE RISHIKIM I LITERATURËS

Abstrakt

Ky artikull paraqet tre raste të pacientëve të diagnostikuar me strumë nodulare toxike të shoqëruar me orbitopatinë e Graves ku njëri prej tyre kishte karcinomë papilare të tiroides.
Hyrje: Bashkëekzistenca e orbitopatisë e Graves dhe struma nodulare toxike është një dukuri e rrallë. Ndërsa hipertiroidizmi besohet se mbron nga kanceri i tiroides, studimet e fundit sugjerojnë se incidenca e tumoreve malinje në strumë nodulare toxike nuk është aq e ulët sa mendohej më parë.
Metodat: Përfshijnë gjetjet klinike, laboratorike dhe radiologjike, konfirmuar me shintigrafi të tiroides 99m Tc për strumë nodulare toxike. Diskutohet menaxhimi i suksesshëm i orbitopatisë së Graves dhe sfidat e trajtimit të strumës nodulare toxike dhe orbitopatinë e Graves njëkohësisht.
Rezultatet: Të tre rastet u paraqiten me hipertiroidizëm dhe orbitopatinë e Graves, ku dy iu nënshtruan tiroidektomisë totale, ku biopsia post operatore zbuloi karcinomë papilare të tiroides në një rast, brenda adenomes toksike. Pacienti i tretë zgjodhi trajtimin me methimazol. Diskutohet menaxhimi i suksesshëm i orbitopatisë Graves dhe sfidat e trajtimit të strumës nodulare toxike dhe orbitopatisë Graves njëkohësisht.
Përfundimi: Struma nodulare toxike e shoqëruar me oftalmopati infiltrative përfaqëson shfaqjen e Semundjen së Graves, e konfirmuar nga antitrupat anti receptorë të tirotropinës. Ndërhyrja kirurgjikale konsiderohet e rëndësishme, veçanërisht në rastet kur struma nodulare toxike bashkëjeton me orbitopatinë e Graves. Artikulli nënvizon rëndësinë e një qasjeje gjithëpërfshirëse, duke përfshirë trajtimet kirurgjikale dhe mjekësore të përshtatura, për rezultate të suksesshme, në raste të tilla komplekse.

Fjalë kyçe: Struma nodulare hiperfunksionante, Graves' Orbitopati, carcinoma papilare e tiroides, antitrupat e receptorit të hormonit stimulus të tiroides.

Introduction

Graves' disease (GD) may initially manifest or develop in a multinodular gland, confirmed by the presence of antibodies to the thyrotropin receptor (TSH-R Ab). Toxic nodular goiter (TNG) is rarely accompanied by infiltrative ophthalmopathy. When both conditions coexist, it typically signifies the emergence of GD (1). Several authors have historically posited that hyperthyroidism protects against thyroid cancer, asserting that the incidence of malignancy is lower in patients with TNG, compared to those with non-TNG (2-4). However, recent studies challenge this belief, reporting that the incidence of malignancy in TNG is not as low as previously thought (5- 11).
Thyrotropin-suppression therapy in euthyroid patients with thyroid autonomous functioning nodules, aimed at reducing multinodular goiter, is usually minimally effective and carries the risk of inducing thyrotoxicosis. There is no conclusive evidence that long-term thyroxine therapy alters the natural course of multinodular goiter, and randomized, placebo-controlled

trials with objective volume measurements are scarce (12- 16). Notwithstanding, approximately half of clinicians in the USA and Europe still employ this treatment. In this report, we present three cases of TNG associated with Graves' Orbitopati (GO). Remarkably, one of these cases was discovered to have papillary thyroid carcinoma (PTC) within the hyperfunctioning nodule.

Case 1

A 68-year-old white woman presented to our endocrinology clinic, with a 6-month history of weight loss (13 kg), nervousness, insomnia, palpitations, fatigue, tremors, and left eye complaints for two months. On physical examination: Height: 162 cm, Weight 67 kg, Blood Pressure (BP): 130/80, Tachycardia, (Pulse: 101/min, regular). Thyroid gland: Palpable nodule in the left lobe; non-suspicious lymph nodes identified clinically. Lungs and abdomen: Normal, Left Eye Examination: Proptosis, eyelid swelling, Redness of the eyelids, Mild conjunctival redness, Clinical Activity Score (CAS): 3 (0-7), Left palpable thyroid nodule, non-tender, with no suspicious lymph nodes identified clinically. Past medical history was unremarkable, with no history of neck irradiation. Family history was also unremarkable. Thyroid ultrasound revealed multiple nodules, with the dominant palpable nodule in the left lobe measuring 3.5 x 4 x 4 cm, hyperechoic with a hypoechoic halo, irregular borders, and perivascular blood flow. Additionally, two similar nodules (heterogeneous structure with irregular borders) were identified, one in the right lobe and the other in the left near the dominant nodule (Fig. 1).

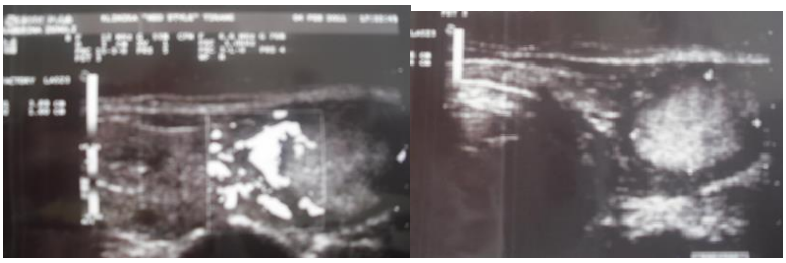


Figure 1: Sonogram shows a solid nodule that is hyperechoic with a hypoechoic thick halo in the left thyroid lobe, exhibiting irregular borders and perinodular blood flow.

A 99m Tc thyroid scintigraphy revealed a "hot" nodule in the left thyroid lobe and suppressed right lobe. (Fig. 2).

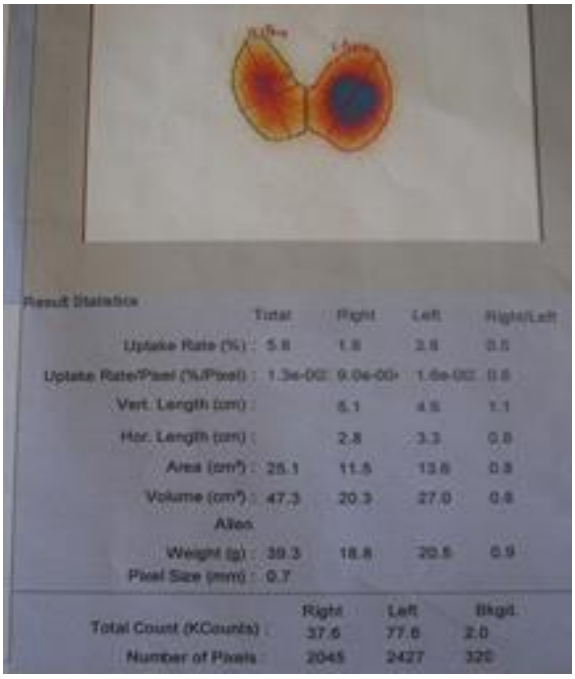


Figure 2: 99mTc thyroid scintigraphy reveals a "hot" nodule in the left thyroid lobe and a suppressed right lobe with high total uptake.

Assessment of thyroid functional status revealed a suppressed thyroid-stimulating hormone (TSH) <0.005 (0.27-4.2) mIU/l, free thyroxine (fT4) 21.88 (2-6.8), and TSH-R Ab 4.0 (<1) UI/ml. Treatment commenced with methimazole 40 mg daily and orally tapered prednisone 30 mg daily (0.5mg per body weight kg), along with artificial tears to protect the left eye from local damage. Once euthyroid and improved regarding eye manifestations, she underwent a total thyroidectomy. Biopsy of the dominant nodule resulted in PTC, follicular variant, and another area near the nodule with PTC Post-surgery, she started hormone replacement treatment with levothyroxine, a suppressive dose according to ATA protocols for thyroid cancer. However, four months later, she experienced a recurrence of signs and symptoms of left eye orbitopathy: inconstant diplopia, proptosis (23.5 mm in the left eye, measured using Hertel exophthalmometer), and inflammatory changes: swelling and redness of the eyelids, redness of the conjunctiva, chemosis, and pain with eye movement during the last weeks. Orbit MRI revealed enlargement of medial rectus and inferior oblique muscles, and hypertrophy of orbital fat (Fig. 3).

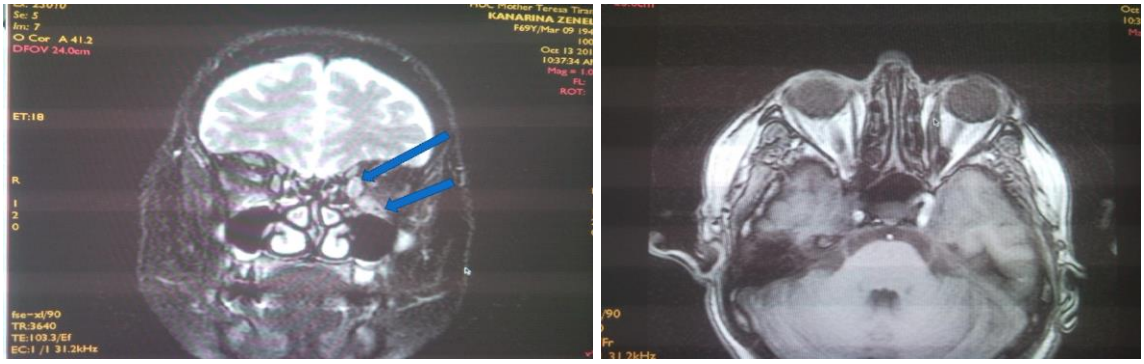


Figure 3: Orbit MRI revealed enlargement of medial rectus and inferior oblique muscles and hypertrophy of orbital fat.

Following the recurrence of left eye orbitopathy signs and symptoms, the patient received four intravenous pulses of glucocorticoid (a total methylprednisolone acetate dose of 2 g, 500 mg per pulse once a day over 4 days). This was administered along with local treatment, including artificial tears, lubricating cream, and sunglasses. Subsequently, she showed improvement in signs and symptoms of orbitopathy, allowing for a transition to orally taper low doses of prednisone at 30 mg daily. Two months later, a follow-up Orbit MRI revealed normal dimensions of orbit muscles with hypertrophy of orbital fat. At this point, her thyroid function tests indicated a TSH level of 1.98 (normal range: 0.27-4.2) mIU/l and TSH-R Ab 1.0 (N <1.0). She continued to maintain an euthyroid state with inconstant diplopia and inactive moderate GO. Ongoing monitoring and management were implemented to ensure sustained improvement in thyroid function and orbitopathy symptoms.

Case 2

A 48-year-old white woman was admitted to the Department of Endocrinology in April 2019, presenting complaints of right eye vision blurring, fatigue, palpitation, insomnia, heat intolerance, and tremors. Physical examination revealed a thyroid gland with a palpable nodule in the right lobe, no lymphadenopathy, and notable proptosis (26 mm) with inflammatory changes in the right eye. Her CAS was 6, and the left eye showed proptosis of 17 mm. Laboratory results indicated elevated FT4: 4.25 (0.75-1.70) ng/dl] and suppressed TSH 0.07 (0.27 -4.2) mIU/L. TSH-RAb 2.6 (<1) ui/l, while antithyroglobulin antibodies (anti-TG) and thyroid peroxide antibodies (anti-TPO) were negative. Thyroid ultrasonography revealed an isoechoic structure in both lobes with two nodules in the right lobe. The big one was 1.48x1.85 cm and the other of 0.85 x 0.64 cm (Fig. 4).

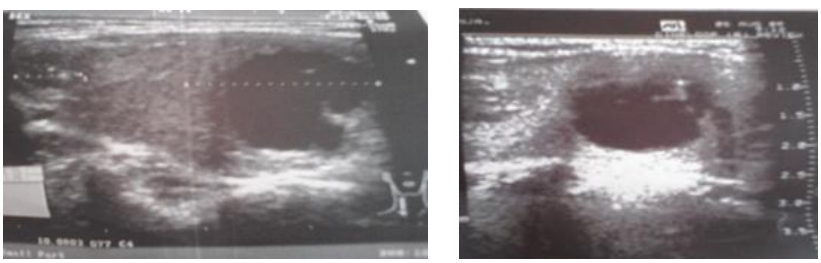


Figure 4: Thyroid gland images reveal the right lobe with a nodule exhibiting anechoic structure and dimensions of 1.48 x 1.85 cm, along with another heterogeneous nodule measuring 0.85 x 0.64 cm.

The 99mTc thyroid scintigraphy displays two "hot" nodules in the right thyroid lobe and suppressed left lobe, with low total uptake (Fig. 5)

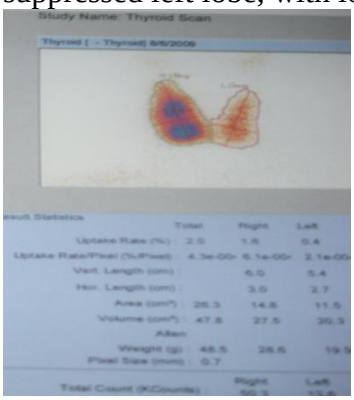


Figure 5: Thyroid Scintigraphy with 99m Tc, reveals two hot nodules in the right lobe and suppressed left lobe.

An orbit MRI with gadolinium documented enlargement of superior and lateral recti muscles and supraorbital soft tissues of the right eye (Fig. 6).

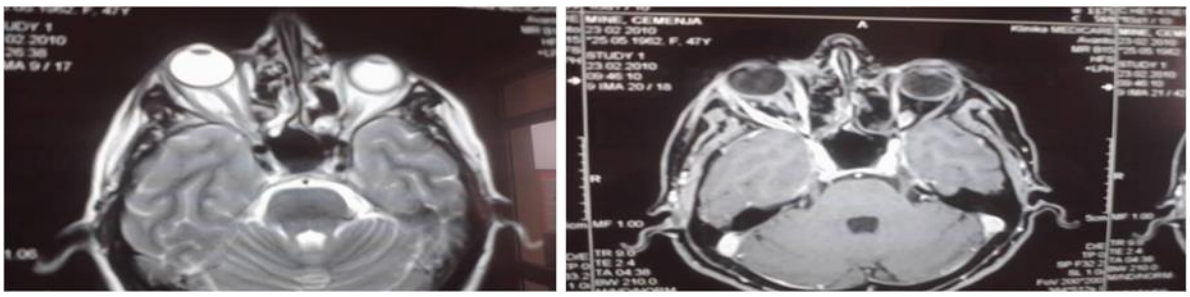


Figure 6: Orbit MRI reveals enlargement of lateral recti muscles of the right eye.

The patient had a history of non-TNG diagnosed 6 years ago, initially managed with levothyroxine treatment. However, after three years of therapy, she developed right eye GO associated with thyrotoxic symptoms secondary to TNG. Following evaluation, levothyroxine was discontinued, and she was initiated on 20 mg methimazole/per day and orally tapered prednisone (0.5mg per body weight kg) for GO. Despite initial improvement, a recurrence of orbitopathy symptoms led to her referral to an endocrinology service. The thyroid function tests showed a TSH of 0.868 (0.27-4.8) µIU/m, FT4 1.46 (0.75-1.70) ng/dl, and a CAS > 3 (7 points). The patient was restarted glucocorticoid therapy but intravenous pulses of methylprednisolone acetate. A total dose of 4.5 g over 12 weeks, six weeks with 500 mg intravenous per week and six weeks with 250 mg/per week (according to European Group of Graves Orbitopathy EUGOGO Protocol for GO treatment) and continuing on orally tapered prednisone (30 mg/day). Results of thyroid function tests during follow-up (Table 1).
This treatment resulted in the amelioration of eye manifestations. However, worsening eye motility and reduced visual acuity in the right eye were observed over time. Once euthyroid, the patient underwent total thyroidectomy, starting hormone replacement with levothyroxine, post-surgery. She remained euthyroid, and no detectable thyroid tissue was found on ultrasound. Histopathology examination of thyroid tissue revealed benign pathology.

Table 1: Results of thyroid function investigations during follow-up of case 2.

D/M/Y	TSH (0,27-4,2mIu/l)	Ft4 (0,75-1,70) ng/dl	TSH-RAb (<1) UI/l	TPO-Ab (>75) UI/l
O6/09/20016	1,54	1,40		
08/08/20019	0,007	4,25		
11/02/2020	0,868	1,46		
07/04/2020	0,07	4,25	2,6	19,2
06/07/2020	0,4	4,08 (7-18) pg/ml		
07/09/2020	0,05	10,4 pg/ml		
02/12/2020	3,74	5,6 pg/ml	0,3pg/ml	
21/02/2021	26,1	4,6 pg/ml	0,9 pg/ml	0,6
10/04/2021	2,04	13 pg/ml		

Case 3

A 53-year-old white woman presented with a year-long history of weight loss, tachycardia, and fatigue. On physical examination, both eyes exhibited proptosis (23.5 mm left eye, 24 mm right eye, measured using Hertel exophthalmometer) and inflammatory changes, with a CAS > 3. The orbit MRI revealed enlargement of the inferior, medial, and superior recti muscles (Fig. 7).

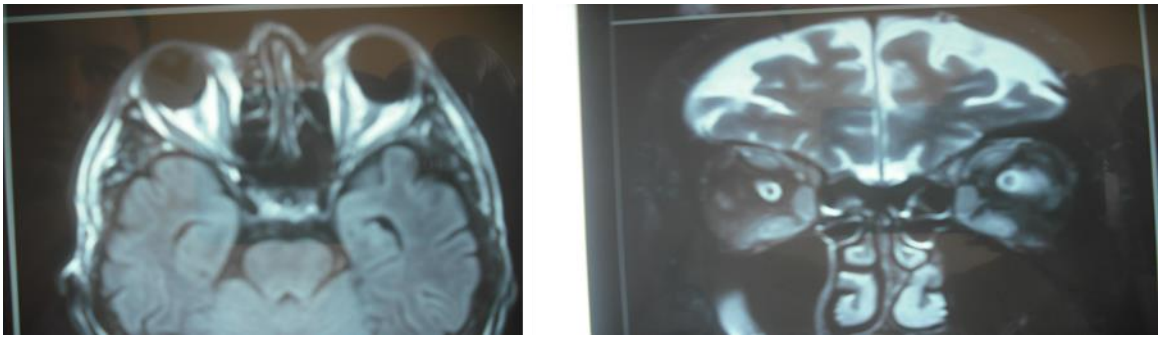


Figure 7: The orbit MRI revealed enlargement of the inferior, medial, and superior recti muscles.

She had a palpable nodule on the right thyroid lobe and bilateral laterocervical palpable lymph nodes, which, upon biopsy, resulted in reactive hyperplasia. Thyroid ultrasound indicated a hyperechoic nodule on the right lobe measuring 2x1.36x1.4 cm and two other hyperechoic nodules on the left lobe with dimensions over 1 cm and under 2 cm. Her 99m Tc thyroid scintigraphy showed a "hot" nodule in the right thyroid lobe and two hot nodules in the left lobe (Fig. 8).

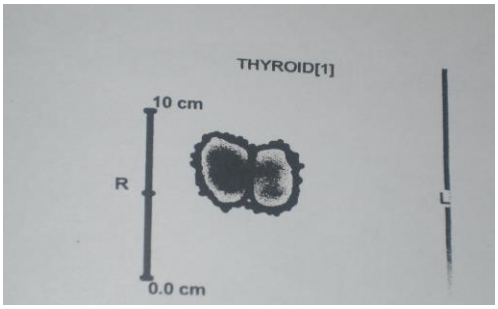


Figure 8: The 99mTc thyroid scintigraphy exhibits a "hot" nodule in the right thyroid lobe and two
additional hot nodules in the left lobe.

Assessment of thyroid functional status revealed a suppressed TSH <0.005 (0.27-4.2) mIU/L], elevated FT4 40.1 pg/ml (normal range 7-18)], and TSH-R Ab1.5 (<1) ui/ml. Treatment was initiated with methimazole (20 mg daily) and orally tapered prednisone (30 mg daily), along with local measures to protect the eyes. Once euthyroid and improved regarding eye manifestations, surgery was proposed as a definitive solution of hyperthyroidism. However, the patient declined, opting to continue being euthyroid under methimazole and maintaining stability regarding ophthalmopathy through local measures.

Discussion:

TNG accompanied by infiltrative ophthalmopathy represents the emergence of GD as confirmed by the presence of TSH-R Ab. Surgical intervention is considered a crucial therapeutic modality, especially in cases where TNG coexists with GO. We conclude by emphasizing the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in these complex cases. Discussion: The coexistence of GD with GO and PTC is considered a rare occurrence. The diagnosis of GO in our three cases was established based on the presence of ophthalmopathy, confirmed by positive serum TSH-R Ab, which are specific indicators of GD. While thyroid nodules are found in 13–20% of all GD (17), the combination of GO and TNG is infrequent, occurring in only 0.05–0.2% of patients with GD (18). Reviewing the literature indicates that incidental thyroid carcinoma in patients undergoing thyroidectomy for a hyperfunctioning nodule, both within and outside the nodule, is not uncommon. In our first patient, unilateral orbitopathy and concomitant hyperthyroidism resulted from an autonomously functioning thyroid nodule. Recent attention has been drawn to the increased risk of malignant thyroid nodules in GD patients, potentially linked to stimulating antibodies promoting cell proliferation (19,20). Consequently, optimizing the therapeutic approach in these patients becomes imperative. In our case, fine needle aspiration cytology was not performed before surgery. Total thyroidectomy was chosen for several reasons: Firstly, although cancer in TNG is rare, reported cases exist (20-22); Secondly, suspicious features on ultrasound images, including irregular borders of the dominant nodule and heterogeneous structure with irregular borders in other nodules; Thirdly, the potential exacerbation of orbitopathy with 131I therapy and finally, the absence of contraindications for surgery. Subsequent biopsy post-total thyroidectomy confirmed the coexistence of PTC in TNG,

supporting our decision for surgery as the optimal therapeutic modality in such cases. Thyrotrophin-suppression therapy in euthyroid patients with thyroid autonomous functioning nodules has limited effectiveness, carrying the risk of inducing thyrotoxicosis. In the second case, after three years of levothyroxine treatment, hyperthyroidism symptoms and unilateral GO emerged. Objective causality assessment suggested a probable relation to long-term levothyroxine use. Coexistence with unilateral orbitopathy was confirmed to be GO through the presence of TSH-R Ab. According to EUGOGO recommendations, intravenous glucocorticoids must be administered as the first-line treatment for moderate to severe and active GO. Oral glucocorticoids are considered less effective than their intravenous counterparts (23,24). Total thyroidectomy was performed due to moderate-severe orbitopathy (given that radioactive iodine treatment might worsen preexisting ophthalmopathy) and to provide a rapid and successful resolution. Post-total thyroidectomy, the patient remained euthyroid on levothyroxine treatment, reinforcing our view that surgery is the optimal therapeutic modality in similar cases.

Conclusion: Toxic nodular goiter accompanied by infiltrative ophthalmopathy represents the emergence of Graves' disease, confirmed by the presence of TSH-R Ab. Surgical intervention is considered a crucial therapeutic modality, especially in cases where toxic nodular goiter coexists with Graves' orbitopathy. The article underscores the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in such complex cases.

References:

1. Williams textbook of endocrinology.eleventh edition Toxic multinodular goiter 2008;337. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6992389/.
2. Vaiana R, Cappelli C, Perini P, Pinelli D, Camoni G, Farfaglia R, et al . Hyperthyroidism and concurrent thyroidcancer. Tumori 1999; 85:247-52. [PUBMED]. https://pubmed.ncbi.nlm.nih.gov/10587026/.
3. Cole WH. Incidence of carcinoma of the thyroid in nodular goiter. Semin Surg Oncol 1991; 7 (2) 613. https://pubmed.ncbi.nlm.nih.gov/2034940/
4. Koh KB, Chang KW. Carcinoma in multinodular goitre. BrJ Surg 1992; 79 (3): 266-7. https://pubmed.ncbi.nlm.nih.gov/1555099/.
5. J Postgrad Med. 2007 Jul-Sep;53(3):157-60.Thyroid cancer in toxic and non-toxic multinodular goiter. https://www.researchgate.net/publication/6139719.
6. Gul K, Di Ri KA, Ki YG, Ersoy PE, Ugras NS, Ozdemi D, et al. Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. Minerva Endocrinol. 2009; 34: 281 - 288. https://pubmed.ncbi.nlm.nih.gov/20046157/.
7. Cakir M, Arici C, Alakus H, Altunbas H, Balci MK, Karayalcin U. Incidental thyroid carcinoma in thyrotoxic patients treated by surgery. Horm Res. 2007; 67: 96 - 99. https://pubmed.ncbi.nlm.nih.gov/17047344/.
8. Phitayakorn R, McHenry CR. Incidental thyroid carcinoma in patients with Graves' disease. AmJSurg. 2008; 195: 292 -297. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10118985/.
9. Alevizaki M, Papageorgiou G, Rentziou G, Saltiki K, Marafelia P, Loukari E, et al. Increasing prevalence of papillary thyroid carcinoma in recent years in Greece: the

majority are incidental.Thyroid. 2009; 19: 749 754. https://pubmed.ncbi.nlm.nih.gov/19534620/.
10. Daumerie C, Ayoubi S, Rahier J, Buysschaert M, Squifflet JP. Prevalence of thyroid cancer in hot nodules. Ann Chir. 1998; 52: 444. https://link.springer.com/article/10.1007/BF03345140.
11. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, et al. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg. 2006; 76: 123 -126. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1445-2197.2006.03667.x
12. Papini E, Petrucci L, Guglielmi R, et al. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. J Clin Endocrinol Metab. 1998 83: 780-783,1998. https://pubmed.ncbi.nlm.nih.gov/9506726/.
13. Csako G, Byrd D, Wesley RA, et al. Assessing the effects of thyroid suppression on benign solitary thyroid nodules: A model for using quantitative research synthesis. Medicine 79: 9-26,2000. https://pubmed.ncbi.nlm.nih.gov/10670406/.
14. Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metab 87: 4154-4159,2002. https://www.ncbi.nlm.nih.gov/books/NBK69003/.
15. Koc M, Ersoz HO, Akpinar I, et al. Effect of low- and high-dose levothyroxine on thyroid nodule volume:acrossover placebo-controlled trial. Clin Endocrinol 57: 621-628,2002, https://pubmed.ncbi.nlm.nih.gov/12390336/.
16. Bonnema SJ, Bennedbaek FN, Wiersinga WM, Hegedus L. Management of the nontoxic multinodular goitre: a European questionnaire study. Clin Endocrinol (Oxf) 53:5-12,2000. https://pubmed.ncbi.nlm.nih.gov/10931075/.
17. Kraimps JL, BouinPineau MH, Marechaud R, et al. Basedow's disease and thyroid nodules. A common association. Ann Chir. 1998; 52: 449-451. https://pubmed.ncbi.nlm.nih.gov/9752485/
18. Smolarz K, Dederichs B, Schicha H. Simultaneous occurrence of Graves' ophthalmopathy and autonomous thyroid nodules. Nuklearmedizin. 1998; 37: 213-217. https://pubmed.ncbi.nlm.nih.gov/9770716/.
19. Papanastasiou L, Vatalas IA, Koutras DA, Mastorakos G. Thyroid autoimmunity in the current iodine environment. Thyroid. 2007; 17: 729-739. https://pubmed.ncbi.nlm.nih.gov/17725430/
20. Valenti TM, Macchia E, Pisa R, et al. Toxic adenoma and papillary thyroid carcinoma in a patient with Graves' disease. J Endocrinol Invest. 1999; 22: 701-704. https://pubmed.ncbi.nlm.nih.gov/10595835/.
21. Majima T, Doi K, Komatsu Y, et al. Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J. 2005; 52: 309-316. https://pubmed.ncbi.nlm.nih.gov/16006725/.
22. Michigishi T, Mizukami Y, Shuke N, et al. An autonomously functioning 5 thyroid carcinoma associated with euthyroid Graves' disease. J Nucl Med. 1992; 33: 2024-2026. https://pubmed.ncbi.nlm.nih.gov/1432166/.

23. Marcocci C, Bartalena L, Tanda ML et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study 86: 3562-3567, 2001, https://pubmed.ncbi.nlm.nih.gov/11502779/.
24. Kahaly GJ, Pitz S, Hommel G et al. Randomized, single-blind trial of intravenous vs oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 90: 5234-5240, 2005. https://pubmed.ncbi.nlm.nih.gov/15998777/.

GENERALIZED PRURITUS INDUCED BY RIVAROXABAN

Petrit Vargu[1], Migena Vargu[2], Sabina Dedej[2], Samuele Vargu[4] , Margarita Gjata Resuli[3].

[1]Cardiologyst,Faculty of Medicine Lecturer
[2]Dermatology Service, University Hospital Center "Mother Teresa", Tirana, Albania
[3]Nephrologist,Head of Internal Medicine, Faculty of Medicine Lecturer
[4]Faculty of Medicine student

Corespondent E-mail: mvargu@yahoo.com

Abstract

Introduction: Oral anticoagulants are essential for preventing stroke and pulmonary embolism in patients with atrial fibrillation. Rivaroxaban, a widely prescribed direct factor Xa inhibitor, has been associated with various dermatologic side effects, including pruritus, although rarely. While cutaneous side effects are relatively uncommon with Rivaroxaban, it is crucial to recognize such potential adverse effects to manage them effectively and maintain patient adherence to anticoagulation therapy. The patient's response to medication change highlights the need for awareness of drug-induced pruritus and the importance of appropriate management strategies.
Case Presentation: This report discusses a 65-year-old male with atrial fibrillation who developed generalized pruritus following the administration of Rivaroxaban. The patient did not have significant cutaneous lesions, known drug or food allergies, or any systemic disease that could explain his symptoms. His condition improved after switching to Apixaban and starting treatment with an oral antihistamine.
Conclusion: Given the impact of pruritus on quality of life and the risk of discontinuing essential medication, identifying the causes of drug-induced pruritus is critical. This case underscores the importance of considering a detailed drug history in patients presenting with unexplained pruritus and suggests that clinicians remain vigilant about the less common side effects of newer anticoagulants like Rivaroxaban. Further research is needed to elucidate the mechanisms underlying drug-induced pruritus and to optimize management strategies for affected patients.

Keyword: anticoagulants, drug -induced pruritus, antihistaminic drugs.

PRURITI I GJENERALIZUAR I INDUKTUAR NGA RIVAROXABAN

Abstrakt

Hyrje: Antikoagulantët oralë janë thelbësorë për parandalimin e insultit cerebral dhe embolise pulmonare, në pacientët me fibrilacion atrial. Rivaroxaban, një frenues i drejtpërdrejtë i faktorit Xa i përshkruar gjerësisht, është shoqëruar me efekte të ndryshme anësore dermatologjike, duke përfshirë pruritin, megjithëse rrallë. Ndërsa efektet anësore të lëkurës janë relativisht të rralla me Rivaroxaban, është thelbësore të njihen këto efekte të mundshme negative, për t'i menaxhuar ato

në mënyrë efektive, dhe për të ruajtur pacientin ndaj terapisë antikoaguluese. Përgjigja e pacientit ndaj ndryshimit të mjekimit nxjerr në pah nevojën për ndërgjegjësim për pruritin e shkaktuar nga medikamentet dhe rëndësinë e strategjive të duhura të menaxhimit.

Prezantimi i rastit: Nje mashkull 65-vjeçar me fibrilacion atrial, zhvilloi prurit të gjeneralizuar pas administrimit të Rivaroxaban. Pacienti nuk kishte lezione të rëndësishme të lëkurës, alergji të njohura ndaj ilaçeve ose ushqimeve, ose ndonjë sëmundje sistemike që mund të shpjegonte simptomat e tij. Gjendja e tij u përmirësua pas kalimit në Apixaban dhe fillimit të trajtimit me antihistaminike orale.

Përfundim: Duke pasur parasysh ndikimin e pruritit në cilësinë e jetës, identifikimi i shkaqeve të pruritit të shkaktuar nga ilaçet është e rëndësishme. Ky rast nënvizon rëndësinë e marrjes parasysh të një historie të detajuar të barnave në pacientët që paraqiten me prurit të pashpjegueshëm dhe sugjeron që mjekët të qëndrojnë vigjilentë për efektet anësore më pak të zakonshme të antikoagulantëve më të rinj si Rivaroxaban. Nevojiten kërkime të mëtejshme për të sqaruar mekanizmat, që qëndrojnë në themel të pruritit të induktuar nga ilaçet dhe për të optimizuar strategjitë e menaxhimit për pacientët e prekur.

Fjalë kyce: astma e rëndë, sëmundje, sindromë, komorbiditet.

Introduction

Oral anticoagulant is an imperative therapy in patients with atrial fibrillation episodes to prevent stroke or pulmonary embolism events (1). Rivaroxaban is one of the most prescribed medications in this category. According to the product monograph, various dermatologic side effects have been reported in the literature, with pruritus being 1.8% of cases (2). Here, we will discuss a case of drug-induced pruritus and proper management with two important implications: safety and improving quality of life.

Case report

We present a case of a 65-year-old male patient with generalized pruritus without significant cutaneous lesions. He was admitted to the Dermatology Service to investigate the causes of his complaints. The patient's history was associated with an intense, generalized pruritus, which he had been suffering from for several months. He stated that these complaints started after the Rivaroxaban administration to treat atrial fibrillation. The pruritus was never associated with hypersensitivity syndrome or angioedema. The patient claimed no known drug or food allergies. His personal history included benign prostatic hyperplasia, and he was currently undergoing treatment with Tamsulosin and Dutasteride. His physical examination was normal except for post-inflammatory hyperpigmentation and excoriations. Otherwise, the patient underwent laboratory and imaging examinations to exclude systemic diseases as potential and serious causes of pruritus. According to the hematologist, the complete blood count revealed anemia and some alterations of leukocytes and thrombocytes, which were unrelated to any malignant hematology disorder. The renal, hepatic, thyroid, and autoimmune results were within the

reference range. Chest radiography, prostate, and abdominal echography found no structural abnormalities. Since we could not find any abnormality or other drug to explain the itching, we were convinced it was a consequence of the newly started medication. We asked the cardiologist to switch the oral anticoagulant in order to maintain a safe profile of his cardiac disease as well as to stop the itching process. After the Apixaban and oral antihistamine administration, the complaints were relieved.

Discussion

Rivaroxaban is the first agent available within a new class of anticoagulants called direct factor Xa inhibitors. It is preferred to warfarin because of its better pharmacokinetics that allows simplified management (3). Cutaneous manifestations related to Rivaroxaban are relatively uncommon. In the literature, we could find various studies that report accompanying dermatological manifestations such as pemphigoid bullous-like lesions (4), hypersensitivity syndrome (5), DRESS syndrome (6), erythema multimorfe (7), and serum sickness reaction (8).
Drug-induced pruritus, often experienced as an uncontrollable need to scratch, is triggered by a variety of medications and accounts for about 5-10% of all reported drug side effects. Commonly referred to as itching, pruritus can significantly lower life quality and add psychological, social, and economic strains on affected individuals. Addressing pruritus is crucial because it can increase the risk of patients stopping their treatment, which can worsen their primary health condition (9-11).
In the case described, Rivaroxaban appears to be the sole likely cause of the generalized pruritus. The patient had been taking Tamsulosin and Dutasteride for a period of time and had not reported any adverse effects. While Dutasteride is not commonly associated with causing pruritus, Tamsulosin has been infrequently linked to allergic dermatitis that includes pruritus as a symptom. Moreover, the symptoms of itching improved after discontinuing Rivaroxaban. Thus, other medications being used concurrently were ruled out as culprit agents. Furthermore, the Naranjo Adverse Drug Reaction scored 5 points, which makes the causality of medication-induced pruritus probable (12).
There are limited reports connecting Rivaroxaban to pruritus. Nassif et al. reported instances of two male patients, both older than 60 and with atrial fibrillation, who experienced pruritus following the use of Rivaroxaban (13). Similar to the situation described in our report, their treatment was changed to Apixaban, supplemented with an oral antihistamine, which led to an improvement in their pruritus symptoms.
We encouraged our patient to report any issues, noting that Apixaban has been linked to cutaneous hypersensitivity syndrome in some cases (14). Six months after switching to Apixaban, the patient has not experienced any adverse effects.
Gaining a deeper understanding of the causes of drug-induced pruritus is critical for improving clinical management and treatment decisions. However, the exact mechanisms causing drug-induced pruritus, including Rivaroxaban, remain unclear. Further researches are needed to explain the pathological mechanisms underlying pruritus in these patients.

Conclusion

Given the impact of pruritus on quality of life and the risk of discontinuing essential medication, identifying the causes of drug-induced pruritus is critical. This case underscores the importance

of considering a detailed drug history in patients presenting with unexplained pruritus and suggests that clinicians remain vigilant about the less common side effects of newer anticoagulants like Rivaroxaban. Further research is needed to elucidate the mechanisms underlying drug-induced pruritus and to optimize management strategies for affected patients.

Conflict of Interest. None.

References

1. Chen A, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. J Am Heart Assoc. 2020;9(13): e017559.
2. Xarelto (rivaroxaban) [packageinsert]. Ontario (CA): Bayer Inc; 2015.
3. Smythe MA, Fanikos J, Gulseth MP, et al. Rivaroxaban: practical considerations for ensuring safety and efficacy. Pharmacotherapy. 2013;33(11):1223-1245.
4. Ferreira C, Oliveira A, Furtado A, Rocha N, Ribeiro JA. Bullous Pemphigoid-like Skin Eruption during Treatment with Rivaroxaban: A Clinical Case Study. Eur J Case Rep Intern Med. 2018;5(3):000724. Published 2018 Mar 21.
5. Chiasson CO, Canneva A, Roy FO, Doré M. Rivaroxaban-Induced Hypersensitivity Syndrome. Can J Hosp Pharm. 2017;70(4):301-304.
6. Radu C, Barnig C, de Blay F. Rivaroxaban-Induced Drug Reaction With Eosinophilia and Systemic Symptoms. J Investig Allergol Clin Immunol. 2016;26(2):124-126.
7. Cao Z, Fu Z, Liu Y, et al. Probable rivaroxaban-induced erythema multiforme in children: A case report. Saudi Pharm J. 2023;31(11):101801.
8. Snyder DJ, Matusik FB. Rivaroxaban-induced serum sickness after total knee arthroplasty. Am J Health Syst Pharm. 2015;72(18):1567-1571.
9. Nakao Y, Asada M, Uesawa Y. Comprehensive Study of Drug-Induced Pruritus Based on Adverse Drug Reaction Report Database. Pharmaceuticals (Basel). 2023;16(10):1500.
10. Reich, A.; Ständer, S.; Szepietowski, J. Drug-induced Pruritus: A Review. Acta Derm. Venereol. 2009, 89, 236–244.
11. Whang, K.A.; Khanna, R.; Williams, K.A.; Mahadevan, V.; Semenov, Y.; Kwatra, S.G. Health-Related QOL and Economic Burden of Chronic Pruritus. J. Investig. Dermatol. 2020, 141, 754–760.e1.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245.
13. Nassif D, Weatherton N, Nassif A. Medication-Induced Pruritus From Direct Oral Anticoagulants. Fed Pract. 2017;34(12):36-37.
14. Isaq NA, Vinson WM, Rahnama-Moghadam S. Apixaban-induced cutaneous hypersensitivity: a case series with evidence of cross-reactivity. Dermatol Online J. 2020;26(10):13030/qt1r37k272.

A RARE CASE OF PULMONARY ASPERGILLOSIS, WHAT TO TAKE INTO CONSIDERATION

Serxho Golgota[1], Kristi Reveli[1], Eritjan Tashi[1], Marsel Broqi[1], Anxhela Papa[2], Fadil Gradica[1], Fabiola Bali[1], Arjan Mezini[1].
[1]University Hospital of Lung Diseases "Shefqet Ndroqi"
[2]Regional Hospital of Berat
Correspondent e-mail: serxhogolgota@live.com

Abstract

Introduction: Pulmonary aspergillosis is a significant medical complication for individuals with chronic lung diseases or compromised immune systems. Prompt and accurate intervention is crucial for treating this disease. This study aims to document a clinical case of a patient with pulmonary aspergillosis, who underwent a prolonged period of suspicion for this disease and unfortunately did not receive appropriate treatment. Through the analysis of the case and the use of various diagnostic methods, the importance of an accurate diagnosis and prompt treatment for this pathology is emphasized.
Methodology: The patient considered for this study faced suspicions of pulmonary aspergillosis for a long period. To confirm the diagnosis and plan treatment, a series of methods were used. These include computed tomography of the chest to identify pulmonary opacities, sputum examination to identify Aspergillus spp., as well as blood tests to assess IgE levels. Additionally, a bronchial secretion culture was performed to identify potential causative agents of the infection. Furthermore, scientific literature was consulted to support the diagnosis and treatment of the patient.
Results: The analyses conducted revealed two pulmonary opacities in the patient's chest, which were confirmed as Aspergillus spp. infection through sputum examination and bronchial secretion culture. Additionally, an elevated level of serum IgE was observed, another possible indication of pulmonary aspergillosis. Based on these results, a diagnosis of pulmonary aspergillosis was made, and it was decided that the patient should undergo surgical treatment.
Conclusion: This case study highlights the importance of a careful and comprehensive approach to the diagnosis and treatment of pulmonary aspergillosis. By utilizing a wide range of diagnostic methods and consulting scientific literature, the successful diagnosis and treatment of the patient commend a joint effort of medicine to address this significant disease. This case also underscores the need for heightened awareness of pulmonary aspergillosis in patients with chronic lung diseases or compromised immune systems.

Keywords: Pulmonary aspergillosis, Chronic lung disease, diagnosis, treatment

NJË RAST I RRALLË I ASPERGILOZËS PULMONARE, ÇFARË DUHET MARRË NË KONSIDERATË

Abstrakt

Hyrja: Aspergilloza pulmonare është një komplikacion i rëndësishëm mjekësor për individët me sëmundje pulmonare kronike ose sistem imunitar të kompromentuar. Ndërhyrja e shpejtë dhe e saktë është thelbësore për trajtimin e kësaj sëmundjeje. Ky studim synon të paraqesë një rast klinik të një pacienteje me aspergjilozë pulmonare, e cila përjetoi një histori të gjatë të dyshimit për këtë sëmundje dhe për fat të keq nuk kishte marrë trajtim të përshtatshëm. Përmes analizës së rastit dhe përdorimit të metodave diagnostike të ndryshme, synohet të theksohet rëndësia e një diagnoze të saktë dhe trajtim të shpejtë për këtë patologji.

Metodologjia: Pacientja e konsideruar për këtë studim u përball me dyshime për aspergjilozë pulmonare për një periudhë të gjatë. Për të konfirmuar diagnozën dhe për të planifikuar trajtimin, u përdorën një sërë metodash. Këto përfshijnë: tomografinë e kompjuterizuar të toraksit për identifikimin e opaciteteve pulmonare, ekzaminimin e sputumit për identifikimin e Aspergillus spp., si dhe analizat e gjakut për të vlerësuar nivelet e IgE. Po ashtu, u bë edhe një kulturë e sekrecioneve bronkiale për të identifikuar shkaktarët e mundshëm të infeksionit. Përveç kësaj, u konsultua literatura shkencore për të mbështetur diagnozën dhe trajtimin e pacientes.

Rezultatet: Analizat e kryera zbuluan dy opacitete pulmonare në toraksin e pacientes, të cilat u konfirmuan si infeksion me Aspergillus spp. përmes ekzaminimit të sputumit dhe kulturës së sekrecioneve bronkiale. Në plus, u vërejt një nivel i rritur i IgE serike, një tjetër indikacion i mundshëm i aspergjilozës pulmonare. Bazuar në këto rezultate, u bë diagnoza e aspergjilozës pulmonare dhe u vendos që pacientja të trajtohej kirurgjikisht.

Konkluzioni: Ky rast studimi thekson rëndësinë e një përqasje të kujdesshme dhe të plotë në diagnozën dhe trajtimin e aspergilozës pulmonare. Duke përdorur një gamë të gjerë metodash diagnostike dhe duke konsultuar literaturën shkencore, diagnoza e suksesshme dhe trajtimi i pacientes përshëndet një përpjekje të përbashkët të mjekësisë për të trajtuar këtë sëmundje të rëndësishme. Ky rast gjithashtu thekson nevojën për një ndjeshmëri të lartë ndaj aspergilozës pulmonare tek pacientët me sëmundje kronike të mushkërive ose sisteme imunitare të dobësuar.

Fjale kyçe: aspergiloza pulmonare, sëmundjet pulmonare kronike, diagnoza, trajtimi

Introduction

Pulmonary aspergillosis is an infection or allergic reaction caused by various types of fungal organisms (most commonly Aspergillus fumigatus) (1). Individuals at higher risk of developing this pathology are those with chronic lung diseases (pre-existing cavity lesions) and compromised immunity. The annual incidence of bronchopulmonary aspergillosis is 1-2 cases per 100,000 population (2). The manifestations of the disease include: simple bronchial colonization, allergic bronchopulmonary aspergillosis, aspergilloma, bronchocentric granulomatosis, extrinsic allergic alveolitis, or invasive pulmonary aspergillosis (3).

Methodology and Results: This clinical case presents a 61-year-old patient who presents with a several-year history of dry cough, chest discomfort, and body weakness. These symptoms have worsened recently, leading her to seek medical attention at the hospital. The patient reports being suspected of Pulmonary Aspergilloma since 2012 (Figure 1), for which several imaging and

laboratory examinations have been conducted over the years, but despite these, she has not received treatment for Aspergilloma.
The patient reports no chronic pulmonary pathology. She is readmitted to the pulmonology service for further examinations.

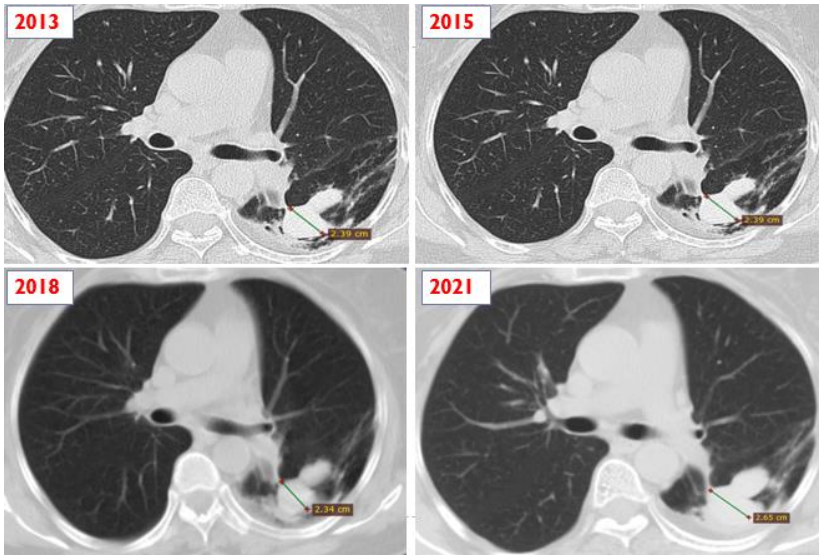


Figure 1: Imaging evolution of the pulmonary lesion over the years.

In the computed tomography of the thorax, the following observations are noted: Central positioning of the mediastinum, without apparent lymphadenopathy. Two nodular pulmonary opacities in the left upper lobe, with pleural thickening and minimal pleural fluid at this level.

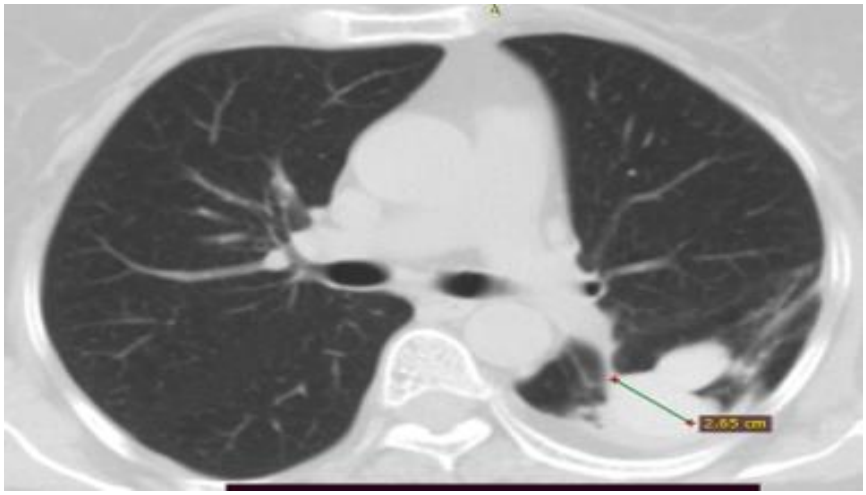


Figure 2: Radiological frame at the time of the last hospitalization.

Examination of sputum for eosinophils is performed, but Aspergillus spp. as well as numerous neutrophils are evident. Serum IgE measurement results in 118.1 IU/mL (normal <100 IU/ml). During the endoscopic examination, hyperemic mucosa is observed in the trachea, with mobile and stiff tracheal carina, while primary, lobar, and segmental bronchi exhibit fragile hyperemic mucosa upon touch, with mucoid secretions freely aspirated from the depth. Lavage for Bacillus Koch (BK) and mycotic lavage in the left hemithorax were performed. Bronchial lavage fungal culture resulted POSITIVE for Aspergillus flavus and Candida Glabrata. Based on the above examinations, the diagnosis is established: Pulmonary aspergillosis, and in general consultation with the heads of the service and thoracic surgeons, the patient is indicated for surgical intervention, and thoracotomy is planned for the removal of Pulmonary Aspergilloma. The surgery was successful without postoperative complications.

Discussion: Despite suspicion for many years as Aspergillosis, the patient's diagnosis was never concluded due to the lack of laboratory and endoscopic examinations. The diagnosis of the pathology is made through serum IgE measurement, skin tests against Aspergillus spp., bronchial secretion culture, and imaging examinations. Treatment varies according to the manifestations and is represented by treatment with antifungals, corticosteroids, or surgical interventions (4,5).
Pulmonary aspergillosis encompasses a range of diseases caused by the fungus Aspergillus, which includes non-invasive forms like aspergilloma and invasive forms such as invasive pulmonary aspergillosis (IPA). The case presents a long-standing suspicion of pulmonary aspergilloma in a patient who experienced progressive symptoms over several years.
The diverse manifestations of pulmonary aspergillosis range from simple colonization to invasive diseases, depending on the host's immune status and lung condition. Aspergilloma, the most common form of pulmonary aspergillosis, often occurs in pre-existing lung cavities and can lead to significant morbidity if not diagnosed and managed properly. Diagnosis generally requires radiographic, serologic, or microbiologic evidence of Aspergillus infection (6).
Surgical intervention remains a primary treatment for aspergilloma, but it carries risks of high mortality and morbidity. For patients unsuitable for surgery, systemic antifungal therapy with azoles such as voriconazole has shown effectiveness in treating chronic pulmonary aspergillosis (CPA). Voriconazole treatment has resulted in improved symptoms and eradication of the fungus in many cases, though some patients may experience side effects (7). Additionally, guidelines recommend long-term oral antifungal therapy to prevent progression and manage symptoms in chronic cases (8). The resistance to antifungal agents and the need for prolonged treatment highlight the complexity of managing pulmonary aspergillosis. Novel antifungal combinations or new therapeutic agents may be required to improve outcomes in resistant or complex cases (9).

Conclusion

This case exemplifies the challenges in diagnosing and managing pulmonary aspergillosis, particularly in patients who do not present with clear risk factors such as compromised immunity. The need for a comprehensive approach that includes accurate diagnosis, consideration of surgical options, and tailored antifungal therapy is crucial. Effective management often requires a combination of therapies adapted to the severity and form of the disease.

References

1. Moldoveanu B, Gearhart AM, Jalil BA, Saad M, Guardiola JJ. Pulmonary Aspergillosis: Spectrum of Disease. Am J Med Sci. 2021 Apr;361(4):411-419. doi: 10.1016/j.amjms.2020.12.009. Epub 2020 Dec 13. PMID: 33563417.
2. Lamoth F, Calandra T. Pulmonary aspergillosis: diagnosis and treatment. Eur Respir Rev. 2022 Nov 29;31(166):220114. doi: 10.1183/16000617.0114-2022. PMID: 36450372; PMCID: PMC9724826.
3. El-Baba F, Gao Y, Soubani AO. Pulmonary Aspergillosis: What the Generalist Needs to Know. Am J Med. 2020 Jun;133(6):668-674. doi: 10.1016/j.amjmed.2020.02.025. Epub 2020 Mar 30. PMID: 32240631..
4. Zarif A, Thomas A, Vayro A. Chronic Pulmonary Aspergillosis: A Brief Review. Yale J Biol Med. 2021 Dec 29;94(4):673-679. PMID: 34970105; PMCID: PMC8686779.

5. Janssens I, Lambrecht BN, Van Braeckel E. Aspergillus and the Lung. Semin Respir Crit Care Med. 2024 Feb;45(1):3-20. doi: 10.1055/s-0043-1777259. Epub 2024 Jan 29. PMID: 38286136; PMCID: PMC10857890.
6. Lang, M., Lang, A., Chauhan, N., & Gill, A. (2020). Non-surgical treatment options for pulmonary aspergilloma.Respiratory medicine, 164, 105903 . https://doi.org/10.1016/j.rmed.2020.105903.
7. Camuset, J., Nunes, H., Dombret, M., Bergeron, A., Henno, P., Philippe, B., Dauriat, G., Mangiapan, G., Rabbat, A., & Cadranel, J. (2007). Treatment of chronic pulmonary aspergillosis by voriconazole in nonimmunocompromised patients.. Chest, 131 5, 1435-41 . https://doi.org/10.1378/CHEST.06-2441
8. Denning, D., Cadranel, J., Beigelman-Aubry, C., Ader, F., Chakrabarti, A., Blot, S., Ullmann, A., Dimopoulos, G., & Lange, C. (2015). Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. European Respiratory Journal, 47, 45 - 68. https://doi.org/10.1183/13993003.00583-2015.
9. Jenks, J., & Hoenigl, M. (2018). Treatment of Aspergillosis. Journal of Fungi, 4. https://doi.org/10.3390/jof4030098.