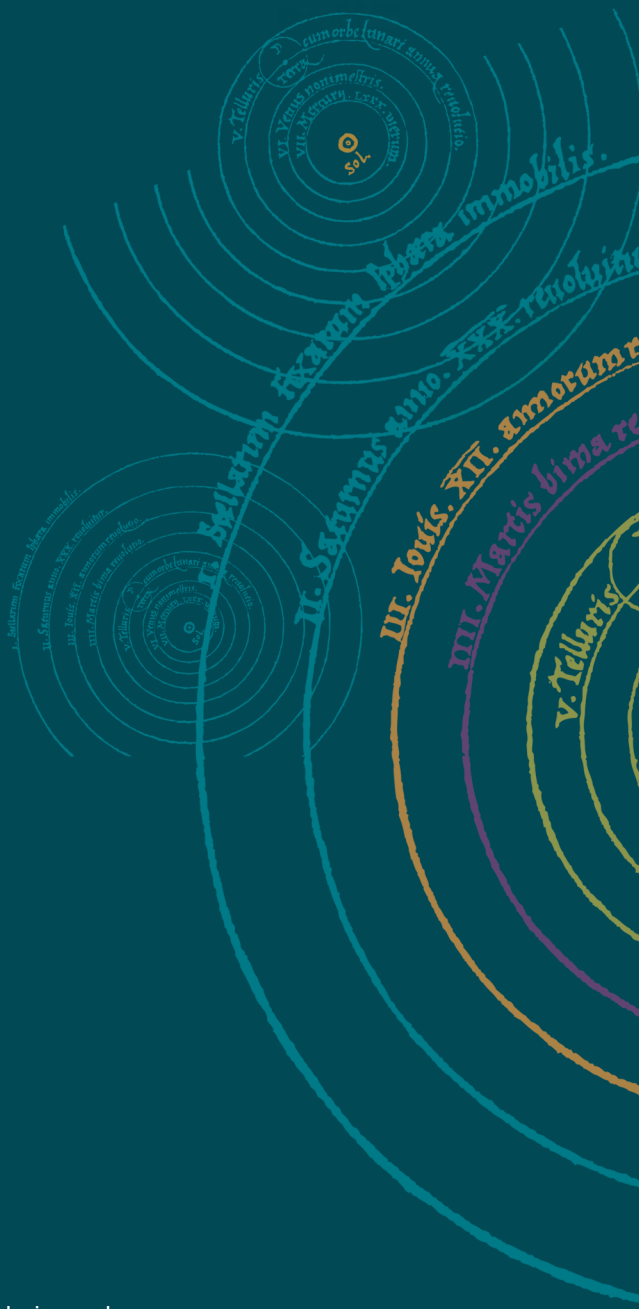
NICOLAUS COPERNICUS
UNIVERSITY
IN TORUŃ

CARDINAL WYSZYŃSKI
UNIVERSITY
IN WARSAW

ISSN 2451–2591
e-ISSN 2451–4101

MEDICAL RESEARCH JOURNAL

2021 Vol. 6 No. 1



VIA MEDICA

www.journals.viamedica.pl/medical_research_journal

NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ
CARDINAL WYSZYŃSKI UNIVERSITY IN WARSAW

MEDICAL RESEARCH JOURNAL

journals.viamedica.pl/medical_research_journal

Medical Research Journal (previously Folia Medica Copernicana, ISSN 2300–5432) is a journal under auspices of Collegium Medicum, Nicolaus Copernicus University and Cardinal Wyszyński University in Warsaw.
The journal is published in English four times per year in electronic form.

Editorial Office Address: Department of Laboratory Medicine, 9 Skłodowskiej-Curie Street, 85–094 Bydgoszcz, Poland; phone (+48 52) 58 540 46

Medical Research Journal (ISSN 2451–2591, e-ISSN 2451-4101) is published by VM Media sp. z o.o., VM Group sp. k., Grupa Via Medica
73 Świętokrzyska Street, 80–180 Gdańsk, Poland
phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60, e-mail: redakcja@viamedica.pl

Medical Research Journal is indexed by Index Copernicus, Ministry of Science and Higher Education, Chemical Abstracts Service (CAS), Ulrich's Periodical Directory, WorldCat and DOAJ (Directory of Open Access Journals).

The Journal has been included in the register of journals and proceedings of international conferences published by The Polish Ministry of Science and Higher Education on 2020 with 20 points awarded.

Index Copernicus Value (ICV) 2019 = 87.98.

Manuscripts should be submitted using online submission system, only.

20-0823.001.001

NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ
CARDINAL WYSZYŃSKI UNIVERSITY IN WARSAW

MEDICAL RESEARCH JOURNAL

CONTENTS

2021; VOLUME 6, NUMBER 1, 1–78

CASE REPORT

LETTERS TO THE EDITOR

VIA MEDICA

INVITED EDITORIAL

Wacław Kochman[1], Salvatore di Somma[2]

[1]The National Institute of Cardiology; Department of Cardiology, Bielanski Hospital, Warsaw, Poland
[2]Postgraduate School of Emergency Medicine, Department of Medical-Surgery Sciences and Translational Medicine, University La Sapienza, Rome; Sant'Andrea Hospital, Rome; GREAT Network Italy

De-escalation of antiplatelet therapy — an approach to improve safety and efficacy of treatment in patients after acute coronary syndrome

Dual antiplatelet treatment (DAPT) with aspirin and P2Y12 inhibitor - clopidogrel has been shown to reduce the risk of ischaemic events in patients after acute coronary syndrome (ACS) [1–3]. Further studies proved the superiority of ticagrelor and prasugrel over clopidogrel in this clinical setting [4–6]. It has been also demonstrated that prolongation of DAPT over one year with lower doses of P2Y12 inhibitor may further improve clinical outcome in patients with previous ACS [7]. At the same time significant improvement in the technology of stents and implantable scaffolds, including design, materials, and antiproliferative agents, occurred resulting in the reduction of thrombogenicity of these devices and allowing the safe shortening of DAPT if necessary [8]. Moreover, changes of platelet reactivity on treatment with P2Y12 inhibitors during the acute phase and the following stable period after ACS [9–18] is an additional factor to be considered. The complexity and ever-better understanding of the pathophysiology of ACS, as well as the ever-wider therapeutic possibilities, require a rethinking of the antiplatelet treatment strategy in this clinical setting.

According to the current guidelines, DAPT with a P2Y12 receptor inhibitor and aspirin is recommended for 12 months to reduce adverse thrombotic events [10, 12, 19, 20]. DAPT can be modified, its duration can be shortened or extended depending on the patient's ischaemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and drugs availability [12]. Termination of treatment with aspirin after 3-6 months after PCI with stent implantation for ACS should be considered, depending on the balance between bleeding and ischaemic risk [19]. De-escalation of DAPT defined as replacing prasugrel or ticagrelor with clopidogrel may be considered in patients after ACS. De-escalation may be unguided, based solely on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on the patient's risk profile and availability of respective assays [19].

The recommendation regarding the de-escalation strategy based on switching a potent P2Y12 receptor inhibitor to clopidogrel is based on the TOPIC study and the TROPICAL-ACS study [19, 21, 22]. In the TOPIC study switching from prasugrel or ticagrelor to clopidogrel one month after ACS was associated with a net clinical benefit mainly driven by bleeding reduction with an unchanged risk of ischaemic events [21]. The TROPICAL-ACS study showed that de-escalation from prasugrel to clopidogrel guided by platelet function testing was non-inferior to standard treatment with prasugrel at 1 year after percutaneous coronary intervention in terms of net clinical benefit in patients with ACS. However, in the de-escalation group, as much as 39% of patients required a switch-back to prasugrel due to insufficient platelet inhibition with clopidogrel defined as HPR [22].

The TWILIGHT study tested another de-escalation strategy comparing DAPT with ticagrelor 90 mg b.i.d. and aspirin versus ticagrelor 90 mg b.i.d. alone was assessed [28]. Monotherapy with ticagrelor resulted in substantially less bleeding events than DAPT arm without ischaemic harm [23].

Recently a new antiplatelet de-escalation approach was proposed in the ELECTRA-SIRIO 2 study (Clinical-

Medical Research Journal 2021; Volume 6, Number 1, 1–3, DOI: DOI: 10.5603/MRJ.a2021.0007, Copyright © 2021 Via Medica, ISSN 2451–2591, e-ISSN 2451-4101
Corresponding author: Wacław Kochman, Department of Cardiology, Bielanski Hospital, Warsaw, Poland, e-mail: w.kochman@icloud.com

Trials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). The study was designed to evaluate the safety and efficacy of ticagrelor dose reduction with or without the continuation of aspirin versus DAPT with standard-dose ticagrelor in ACS patients. The strategy proposed in the ELECTRA-SIRIO 2 study does not require platelet reactivity testing, making de-escalation more feasible for a wide clinical application [24–28]. The study population will comprise 4,500 patients consecutively admitted to the study centres due to ACS, including patients with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina [24]. The intention-to-treat analysis, i.e. with the inclusion of all patients according to the randomly assigned trial group, irrespective of the actual treatment received, is a widely used method in randomized clinical trials, therefore adherence to study medication is a pivotal issue. Poor adherence to the study treatment may lead to serious evaluation bias [29, 30]. The MEDMOTION project involving patients' education, motivation, reminding them to take medications and to attend consecutive medical appointments will be applied to improve adherence to study medication [31–50]. The project includes the diagnosis of study participants concerning their readiness for discharge from the hospital (the Readiness for Hospital Discharge after Myocardial Infarction Scale – RHD-MIS), the risk of non-adherence to the medication (the Adherence in Chronic Diseases Scale, ACDS), and the functioning in disease (the Functioning in Chronic Illness Scale, FCIS). A prespecified sub-analysis of the ELECTRA-SIRIO 2 trial is planned to evaluate the impact of the results of MEDMOTION diagnostic tools on the clinical outcomes [24, 51–59].

The ELECTRA-SIRIO 2 study testing a new approach to treatment de-escalation is expected to provide a new, safer, yet easy-to-apply antiplatelet treatment strategy in a patient after ACS.

References

1. Budaj A, Yusuf S, Mehta SR, et al. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345(7): 494–502, doi: 10.1056/NEJMoa010746, indexed in Pubmed: 11519503.
2. Yusuf S, Mehta SR, Zhao F, et al. Clopidogrel in Unstable angina to prevent Recurrent Events Trial Investigators. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation. 2003; 107(7): 966–972, doi: 10.1161/01.cir.0000051362.96946.15, indexed in Pubmed: 12600908.
3. Adamski P, Adamska U, Ostrowska M, et al. New directions for pharmacotherapy in the treatment of acute coronary syndrome. Expert Opin Pharmacother. 2016; 17(17): 2291–2306, doi: 10.1080/14656566.2016.1241234, indexed in Pubmed: 27677394.
4. Wallentin L, Becker RC, Budaj A, et al. PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/NEJMoa0904327, indexed in Pubmed: 19717846.
5. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators, TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006; 152(4): 627–635, doi: 10.1016/j.ahj.2006.04.012, indexed in Pubmed: 16996826.
6. Navarese EP, Khan SU, James S, et al. Comparative Efficacy and Safety of Oral P2Y Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. Circulation. 2020; 142(2): 150–160, doi: 10.1161/CIRCULATIONAHA.120.046786, indexed in Pubmed: 32468837.
7. Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015; 372(19): 1791–1800, doi: 10.1056/NEJMoa1500857, indexed in Pubmed: 25773268.
8. Ostrowska M, Kubica J, Adamski P, et al. Stratified Approaches to Antiplatelet Therapies Based on Platelet Reactivity Testing. Front Cardiovasc Med. 2019; 6: 176, doi: 10.3389/fcvm.2019.00176, indexed in Pubmed: 31850373.
9. Adamski P, Buszko K, Sikora J, et al. Determinants of high platelet reactivity in patients with acute coronary syndromes treated with ticagrelor. Sci Rep. 2019; 9(1): 3924, doi: 10.1038/s41598-019-40628-0, indexed in Pubmed: 30850677.
10. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39(3): 213–260, doi: 10.1093/eurheartj/ehx419, indexed in Pubmed: 28886622.
11. Kubica J, Adamski P, Niezgoda P, et al. Prolonged antithrombotic therapy in patients after acute coronary syndrome: A critical appraisal of current European Society of Cardiology guidelines. Cardiol J. 2020; 27(6): 661–676, doi: 10.5603/CJ.a2020.0132, indexed in Pubmed: 33073857.
12. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
13. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
14. Kubica J, Adamski P, Ostrowska M, et al. Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION): study protocol for a randomized controlled trial. Trials. 2015; 16: 198, doi: 10.1186/s13063-015-0724-z, indexed in Pubmed: 25925591.
15. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2016; 37(3): 245–252, doi: 10.1093/eurheartj/ehv547, indexed in Pubmed: 26491112.
16. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest. 2016; 46(1): 7–14, doi: 10.1111/eci.12550, indexed in Pubmed: 26449338.
17. Kim HK, Kubica J, Jeong YH. Ticagrelor vs Clopidogrel for Patients With Acute Coronary Syndrome Undergoing Percutaneous Intervention. JAMA. 2021; 325(9): 890, doi: 10.1001/jama.2020.26020, indexed in Pubmed: 33651086.
18. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
19. Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group . 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020 [Epub ahead of print], doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
20. Navarese EP, Wernly B, Lichtenauer M, et al. Dual vs single antiplatelet therapy in patients with lower extremity peripheral artery disease - A meta-analysis. Int J Cardiol. 2018; 269: 292–297, doi: 10.1016/j.ijcard.2018.07.009, indexed in Pubmed: 30045826.

21. Deharo P, Quilici J, Camoin-Jau L, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017; 38(41): 3070–3078, doi: 10.1093/eurheartj/ehx175, indexed in Pubmed: 28510646.
22. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. The Lancet. 2017; 390(10104): 1747–1757, doi: 10.1016/s0140-6736(17)32155-4.
23. Mehran R, Baber U, Sharma S, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. New England Journal of Medicine. 2019; 381(21): 2032–2042, doi: 10.1056/nejmoa1908419.
24. Kubica A, Adamski P, Bączkowska A, et al. The rationale for Multilevel Educational and Motivational Intervention in Patients after Myocardial Infarction (MEDMOTION) project is to support multicentre randomized clinical trial Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome (ELECTRA – SIRIO 2). Medical Research Journal. 2020; 5(4): 244–249, doi: 10.5603/mrj.a2020.0043.
25. Kubica J, Adamski P, Buszko K, et al. Platelet inhibition with standard vs. lower maintenance dose of ticagrelor early after myocardial infarction (ELECTRA): a randomized, open-label, active-controlled pharmacodynamic and pharmacokinetic study. Eur Heart J Cardiovasc Pharmacother. 2019; 5(3): 139–148, doi: 10.1093/ehjcvp/pvz004, indexed in Pubmed: 30689800.
26. Kubica J, Adamski P, Buszko K, et al. Rationale and Design of the Effectiveness of LowEr maintenanCe dose of TicagRelor early After myocardial infarction (ELECTRA) pilot study. Eur Heart J Cardiovasc Pharmacother. 2018; 4(3): 152–157, doi: 10.1093/ehjcvp/pvx032, indexed in Pubmed: 29040445.
27. Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative Efficacy and Safety of Oral P2Y Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. Circulation. 2020; 142(2): 150–160, doi: 10.1161/CIRCULATIONAHA.120.046786, indexed in Pubmed: 32468837.
28. Buszko K, Obońska K, Michalski P, et al. The Adherence Scale in Chronic Diseases (ASCD). The power of knowledge: the key to successful patient — health care provider cooperation. Medical Research Journal. 2016; 1(1): 37–42, doi: 10.5603/mrj.2016.0006.
29. Kubica J, Jaguszewski M. ISAR-REACT 5 - What have we learned? Cardiol J. 2019; 26(5): 427–428, doi: 10.5603/CJ.a2019.0090, indexed in Pubmed: 31536136.
30. Kubica J, Jaguszewski M, Ostrowska M, et al. Creative scientific dispute — different points of view on the protocol and execution of the ISAR-REACT 5 trial. Medical Research Journal. 2020; 5(1): 41–45, doi: 10.5603/mrj.a2020.0008.
31. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. Patient Prefer Adherence. 2018; 12: 333–340, doi: 10.2147/PPA.S150435, indexed in Pubmed: 29551891.
32. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0005, indexed in Pubmed: 32037501.
33. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. Sci Rep. 2020; 10(1): 12028, doi: 10.1038/s41598-020-68915-1, indexed in Pubmed: 32694522.
34. Kubica A, Kosobucka A, Michalski P, et al. The Adherence in Chronic Diseases Scale — a new tool to monitor implementation of a treatment plan. Folia Cardiologica 2017;12:19-26, DOI: 10. 5603/FC. ; 2016: 0000, doi: 10.5603/FC.2016.0000.
35. Kubica A, Kochman W, Bogdan M, et al. The influence of undergone percutaneous coronary interventions, and earlier hospitalizations with myocardial infarction on the level of knowledge and the effectiveness of health education in patients with myocardial infarction. Advances in Interventional Cardiology. 2009; 5: 25–30. doi: 10.1016/j.amjcard.2013.05. 064, indexed in Pubmed. ; 23827404, doi: 10.1016/j.amjcard.2013.05.064.
36. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. Curr Med Res Opin. 2016; 32(8): 1441–1451, doi: 10.1080/03007995.2016.1182901, indexed in Pubmed: 27112628.
37. Adamski P, Ostrowska M, Navarese EP, et al. Pharmacodynamic and clinical efficacy of reduced ticagrelor maintenance doses in patients with coronary artery disease. Curr Med Res Opin. 2021; 37(2): 195–206, doi: 10.1080/03007995.2020.1854207, indexed in Pubmed: 33211543.
38. Kubica A. Self-reported questionnaires for a comprehensive assessment of patients after acute coronary syndrome. Medical Research Journal. 2019; 4(2): 106–109, doi: 10.5603/mrj.a2019.0021.
39. Michalski P, Kasprzak M, Siedlaczek M, et al. The impact of knowledge and effectiveness of educational intervention on readiness for hospital discharge and adherence to therapeutic recommendations in patients with acute coronary syndrome. Medical Research Journal. 2020, doi: 10.5603/mrj.a2020.0023.
40. Kubica A. Rationale of cardiopulmonary resuscitation training as an element of multilevel educational and motivational project (MEDMOTION). Disaster and Emergency Medicine Journal. 2020, doi: 10.5603/demj.a2020.0017.
41. Kubica A, Bączkowska A. Uzasadnienie interwencji motywacyjnych jako kluczowego elementu projektu wielopoziomowej edukacji i motywacji u pacjentów z zawałem serca (MEDMOTION). Folia Cardiologica. 2020; 15(1): 6–10, doi: 10.5603/fc.2020.0003.
42. Buszko K, Pietrzykowski Ł, Michalski P, et al. Validation of the Functioning in Chronic Illness Scale (FCIS). Medical Research Journal. 2018; 3(2): 63–69, doi: 10.5603/mrj.2018.0011.
43. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Knowledge about health and disease in obese patients after myocardial infarction. An observational study. Medical Research Journal. 2018; 2(4): 135–140, doi: 10.5603/mrj.2017.0018.
44. Kubica A, Kosobucka A, Michalski P, et al. Self-reported questionnaires for assessment adherence to treatment in patients with cardiovascular diseases. Medical Research Journal. 2018; 2(4): 115–122, doi: 10.5603/mrj.2017.0015.
45. Kubica A, Gruchała M, Jaguszewski M, et al. Adherence to treatment — a pivotal issue in long-term treatment of patients with cardiovascular diseases. An expert standpoint. Medical Research Journal. 2018; 2(4): 123–127, doi: 10.5603/mrj.2017.0016.
46. Kosobucka A, Kasprzak M, Michalski P, et al. Relation of the Readiness for Hospital Discharge after Myocardial Infarction Scale to socio-demographic and clinical factors. An observational study. Medical Research Journal. 2018; 3(1): 32–37, doi: 10.5603/mrj.2018.0006.
47. Michalski P, Kosobucka A, Pietrzykowski Ł, et al. Effectiveness of therapeutic education in patients with myocardial infarction. Medical Research Journal. 2018; 2(3): 89–96, doi: 10.5603/mrj.2017.0011.
48. Buszko K, Kosobucka A, Michalski P, et al. The readiness for hospital discharge of patients after acute myocardial infarction: a new self-reported questionnaire. Medical Research Journal. 2017; 2(1): 20–28, doi: 10.5603/mrj.2017.0004.
49. Winter MP, Koziński M, Kubica J, et al. Personalized antiplatelet therapy with P2Y12 receptor inhibitors: benefits and pitfalls. Postepy Kardiol Interwencyjnej. 2015; 11(4): 259–280, doi: 10.5114/pwki.2015.55596, indexed in Pubmed: 26677375.
50. Kubica A, Sinkiewicz W, Szymański P, et al. Edukacja zdrowotna w chorobach układu krążenia - możliwości i zagrożenia. Folia Cardiologica Excerpta. 2007; 2: 177.
51. Kubica A. Wybrane problemy prewencji wtórnej u chorych po incydentach wieńcowych. Folia Cardiologica Excerpta. 2008; 3: 366.
52. Kubica A, Obońska K, Kasprzak M, et al. The impact of metabolic syndrome on the antiplatelet effect of clopidogrel and aspirin in patients with acute coronary syndrome. Folia Med Copernicana. 2014; 2: 66–72.
53. Kubica A, Kasprzak M, Obońska K, et al. Impact of health education on adherence to clopidogrel and clinical effectiveness of antiplatelet treatment in patients after myocardial infarction. Medical Research Journal. 2016; 3(4): 154–159, doi: 10.5603/fmc.2015.0010.
54. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. Pharmacology. 2015; 95(1-2): 50–58, doi: 10.1159/000371392, indexed in Pubmed: 25592409.
55. Kubica A. Problems of long-term antiplatelet therapy after coronary stent implantation. Advances in Interventional Cardiology. 2009; 5: 158–161.
56. Kubica A, Grześk G, Sinkiewicz W, et al. Compliance, concordance, adherence in chronic therapy. Folia Cardiol Excerpta. 2010; 5: 54–57.
57. Kubica A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol. 2014; 742: 47–54, doi: 10.1016/j.ejphar.2014.08.009, indexed in Pubmed: 25199965.
58. Kubica A, Obońska K, Kasprzak M, et al. Prediction of high risk of non-adherence to antiplatelet treatment. Kardiol Pol. 2016; 74(1): 61–67, doi: 10.5603/KP.a2015.0117, indexed in Pubmed: 26101025.
59. Kubica A. Collaboration with the patient - a basic condition of therapy effectiveness in coronary artery disease. Chor. Serca Nacz. 2009; 6: 131–134.

VIA MEDICA

ORIGINAL ARTICLE

Abdalla Saad Abdalla Al-Zawi[1,2], Abdul Syed[3], Ali Salih[1], Philip Idaewor[1], Mohamed Elamass[1], Agnieszka Kapturek[4]

[1]Basildon & Thurrock University Hospital, Nethermayne, Basildon, Essex, United Kingdom
[2]School of Medicine, Anglia Ruskin University, Chelmsford, United Kingdom
[3]Southend University Hospital, Prittlewell Chase, United Kingdom
[4]Pratia Medical Research Centre, Skórzewo, Poland

Evaluation of the correlation between Ki-67 proliferative index and the histopathological grade of invasive neoplasms in early breast cancer aged < 70 years of age: a review of 300 cases

Corresponding author:

Abdalla Saad Abdalla Al-Zawi, Basildon & Thurrock University Hospital, Nethermayne, Basildon, Essex, United Kingdom,
e-mail: abdalasaad@gmail.com

Medical Research Journal 2021; Volume 6, Number 1, 4–7
10.5603/MRJ.a2020.0049

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: According to the WHO 2018 reports, breast cancer is the fourth most common cause of cancer deaths worldwide. The breast cancer is recognized as the most common malignancy in the UK, it accounts for about 15% of all newly diagnosed malignancies, followed by prostate (13%), lung (13%), and bowel (11%). Ki-67 proliferative index became a key element in the diagnostic process of breast cancer, in addition to its role as a predictive tool and prognostic marker during the planning of adjuvant therapy as hormonal manipulation of systemic chemotherapy. The study aims to present the correlation analysis between Ki-67 and the different histological grade in breast cancer tumours.

Material and methods: A cohort of 300 patients treated for early breast cancer was included in the study. The demographic data, histopathological subtype, hormonal and HER2 (Human epidermal growth factor receptor-2) receptor status and Ki-67 were analysed. The cut-off point was set at 20% to distinguish "high Ki-67" from "low Ki-67".

Results: About 35% (n = 106) of the cases were grade II with low Ki-67 , 26% (n = 79) grade III with high Ki-67, 19% (n = 56) grade II with high Ki-67, 11% (n = 34) grade I with low Ki-67. The high Ki-67 seen in 135 patients who belong to grade II and III groups (45%), where low Ki-67 in 42% of those cases, however, grade III alone contained more cases of high Ki-67 than any other histological grade group.

Conclusions: A higher tumour histopathologic grade was correlated with higher Ki-67 values (OR = 7.12, 95% CI 16.75–3.03; $p < 0.0001$).

Key words: Ki-67, breast cancer, mammography, chemotherapy, cell cycle

Med Res J 2021; 6 (1): 4–7

Introduction

Worldwide, one in fourteen women will develop breast cancer at the age of 0–79; this figure will rise to one in 9 women in developed countries. WHO reports revealed that breast cancer is the second most frequent malignancy worldwide where lung cancer is the most frequent one. Also, breast cancer is occupying the 5th place in cancer-related mortality list where it comes after lung, colon, stomach and liver cancer. Ki-67 protein proliferative index expression is correlated to the proliferative activity of malignant tumour cells, allowing it to be used as an indicative marker of tumour aggressiveness [1]. Ki-67 expression assessment in the early breast cancer increasingly has become an essential diagnostic tool in adjuvant treatment planning, particularly during the indication of upfront chemotherapy to hormone-sensitive tumour patients. The study aims to present the correlation analysis between Ki-67 and the different histological grade in breast cancer tumours.

Material and methods

A cohort of 300 patients treated for early breast cancer in the period between 2016–2020 was included in the study. Age ranges were between 27–67 years. The demographic data, histopathological subtype, hormonal and HER2 receptor status and Ki-67 were analysed. The Ki-67 results were dichotomized by a cut-off point of 20% into "low Ki-67 ≤ 20%" and "high Ki-67 ≥ 20%".

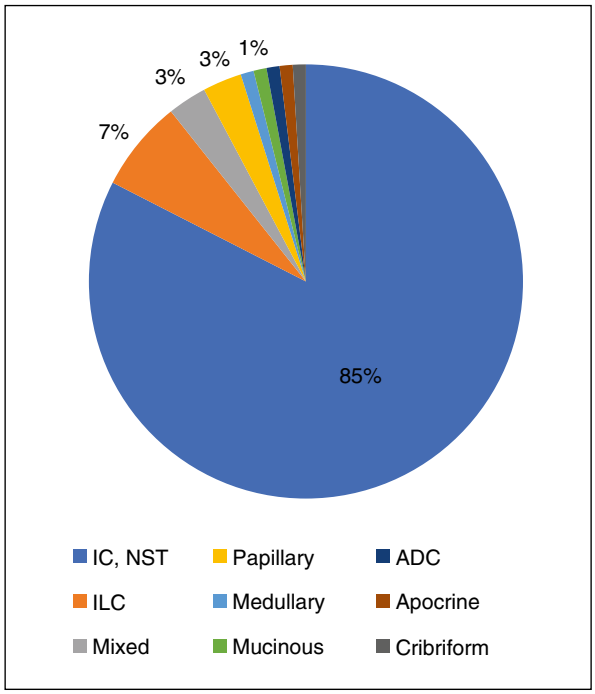


Figure 1. The histopathological subtypes of 300 cases of early breast cancer. IC, NST — invasive ductal carcinoma of no special type; ILC — invasive lobular carcinoma; ADC — adenoid cystic carcinoma

Results

Majority of histological subtype (85%) was invasive carcinoma of no special type (Fig. 1). About 52% of the IC, NST (Invasive carcinoma of no special type) has Ki-67 higher than 20% (Fig. 2). About 35% (n = 106) of the cases were grade II with low Ki-67, 26% (n = 79) grade III with high Ki-67, 19% (n = 56) grade II with high Ki-67, 11% (n = 34) grade I with low Ki-67 (Tab. 1). The high Ki-67 seen in 135 patients who belong to grade II and III groups (45%). The same grade groups (II and III) show low Ki-67 in 42% of the cases, however, grade III alone contains more cases of high Ki-67 than any other histological grade group. Also, after merging Grade I and Grade II tumours in one group, Grade III tumours showed a significant correlation with high Ki-67 (OR = 11.96, 95% CI 8.28–6.94; $p < 0.0001$). Grade III tumours with Ki-67 below 20% were less frequent and seen in only 7% of the cohort, and about 80% of all grade III tumours had a Ki-67 higher than 20%. Most of the grade I tumours was associated with Ki-67 less than 20%, they accounted for about 90% of this group (Fig. 3).

Discussion

In the UK, around 150 new breast cancer cases are detected every day, and this results in around

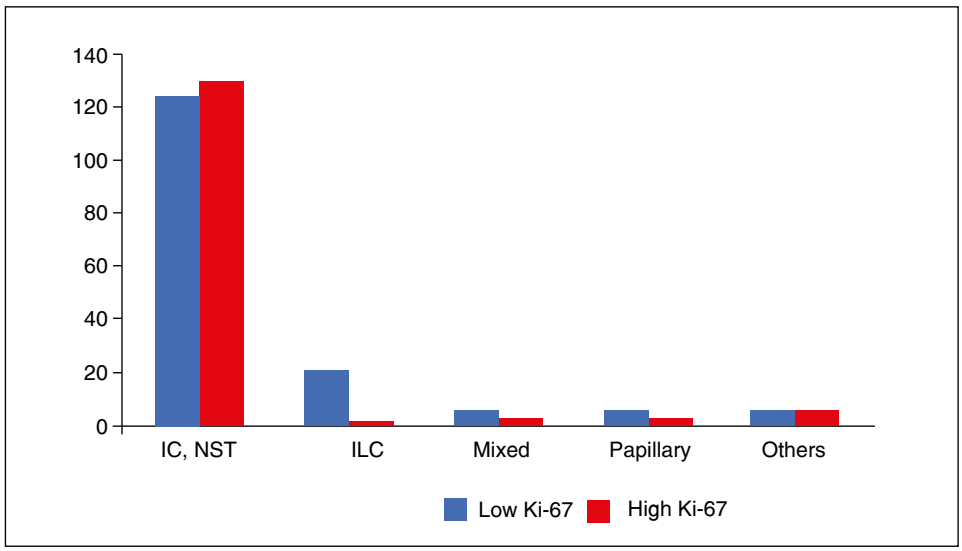


Figure 2. Ki-67 proliferative index among different histopathological subtypes. IC, NST — invasive ductal carcinoma of no special type; ILC — invasive lobular carcinoma; ADC — adenoid cystic carcinoma; Low Ki-67: < 20%; High Ki-67: ≥ 20%

Table 1. Ki-67% expression and tumour grade in 300 cases of breast cancer

Ki-67 level	Grade I	Grade II	Grade III
Low Ki-67 ≤ 20%	11% (34)	35% (106)	07% (21)
High Ki-67 > 20%	01% (4)	18% (56)	26% (79)

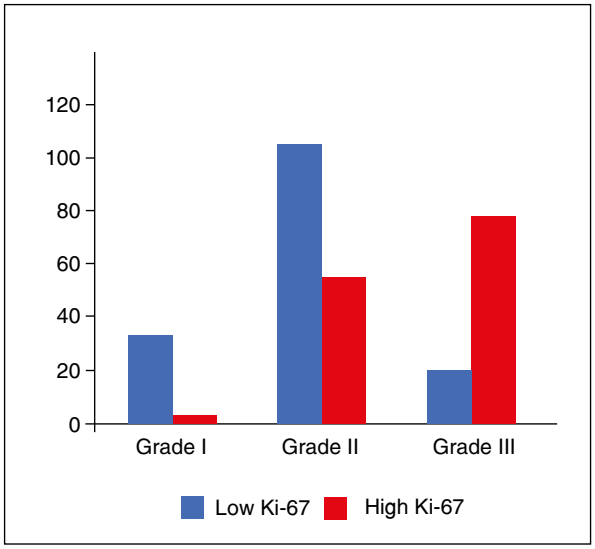


Figure 3. Tumour grade and Ki-67 proliferation index in 300 cases of early breast cancer, higher tumour grades associated with high Ki-67 values. Low Ki-67: < 20%; High Ki-67: > 20%

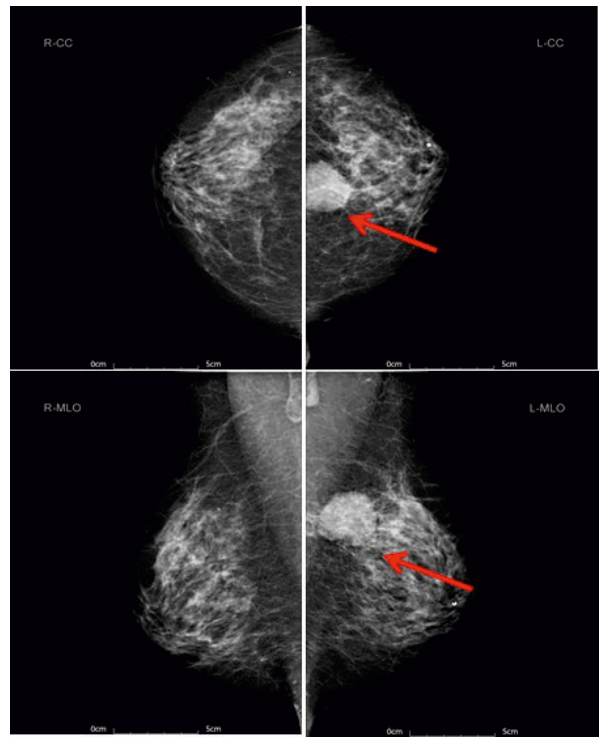


Figure 4. MLO (Mediolateral Oblique) and CC (Craniocaudal) views of the mammogram show a soft tissue density with fairly well-defined margins seen in the left upper inner quadrant close to the midline; the appearance is suspicious and measures about 3.7 cm (red arrow); there are also bilateral benign calcific foci

55,200 new invasive breast cancer cases diagnosed every year and makes it the most common female cancer in the UK. In the United States, breast cancer is also reported to be the most common female cancer, where it accounts for 30% of all newly diagnosed cancer among females [2].

As breast cancer is regarded as a common malignancy worldwide [1], many countries adopted the 3-yearly breast cancer screening mammogram policy (Fig. 4). Every woman which belongs to the age group between 50–70 years is invited for a screening mammogram every 3 years. Every woman above 70 years can still have the screening mammogram every 3 years but won't automatically be invited. This has to be arranged on request through the family doctor or the local breast screening unit. The screening results in increased rates of early diagnosis and allows the clinician to commence the treatment early. This will have a positive impact on the management outcome.

The clinical course of breast invasive carcinoma is very heterogeneous because the variable biomarker factors impact its behaviour. Assessment of clinical and molecular markers is helpful during the decision making when choosing the most appropriate treatment modality. The Ki-67 nuclear antigen was identified in the 1980s, as a protein which is related to cell cycle, and only detected in active dividing cell phases (G1-, S-, G2- and M-phase) but not in quiescent cells (G0 phase) [3]. Ki-67 expression assessment in the early breast cancer increasingly has become an essential diagnostic tool in adjuvant treatment planning, particularly during the indication of upfront chemotherapy to hormone-sensitive tumour patients as it is considered as a dynamic biomarker of treatment efficacy of neoadjuvant therapy [4]. According to the oestrogen receptor (ER), progesterone receptor (PR), and *Human Epidermal Growth Factor Receptor 2* (HER2), the main breast cancer subtypes have been identified. The first subtype is luminal type A, which is ER^+ and/or PR^+/ /$HER2^-$ status, low-grade tumour, and characterised by a good prognosis [5]. The second subtype is lumi-

nal B, it is ER^+ and/or $PR/HER2^-$ status and accounts for about 10% of all breast invasive cancers [6]. The third subtype is luminal B-like (or HER2 positive disease), its immunohistochemistry profile is ER^+, HER2 overexpression or amplification, and any Ki-67or PR [7]. The fourth subtype is HER2 enriched tumour (HER2-2E), they are HER2+, with high expression of ERBB2 and genes of the 17q amplicon, such as GRB7, and low to an intermediate expression of luminal genes such as ESR1 and PGR. Majority of HER2-E tumours are hormone receptor-negative (HR-), however, ~30% are typically HR+ [8]. Patient age, tumour histological subtype, tumour size, female sex hormone receptor, human epidermal growth factor receptor 2 (Her2neu), presence of lymph node disease, presence of genetic mutation as well as Ki-67 has both predictive and prognostic impact on breast cancer management, especially in the loco-regional disease [9, 10]. The histological grade itself is an essential determining factor of breast cancer prognostic tools and is integrated into the staging assessment as in NPI algorithms (Nottingham Prognostic Index) to allow choosing the most optimal therapy for patients with breast cancer. The tumour histological grade is evaluated by examining the morphological features as mitotic count, tubule formation and nuclear pleomorphism. This may highlight the hypothesis of the histological grade indirectly related to Ki-67 based on the mitotic count [2]. This study is limited by the small cohort number, however, the data obtained allow us to suggest the importance of routine use of Ki-67 measurement in the diagnostic workup of breast cancer, to determine breast cancer histological subtypes and also to use it as a prognostic and a predictive tool in the disease management [11, 12]. In the presented study, the correlation between Ki-67 level and the tumour histopathologic grade variables was analysed. Higher tumour histopathologic grade was correlated with higher Ki-67 values. Tumours of grade III with a Ki-67 below 20% were less frequent. On the other hand, most grade I tumours tend to possess Ki-67 below 20%.

Conclusions

In this study, it was observed that Ki-67 is to be considered a valuable biomarker in breast cancer patients. A higher tumour histopathologic grade was correlated with higher Ki-67 levels.

Key points

The Ki-67 level is considered a valuable biomarker in breast cancer management especially in its role as a prognostic indicator. Ki-67 expression is associated with common histopathological parameters as the tumour histological grade, higher ki67 correlates with higher tumour grade (OR = 7.12, 95% CI 16.75–3.03; $p < 0.0001$). Measuring Ki-67 index expression would have a significant impact on adjuvant or neoadjuvant chemotherapy decision.

References

1. Saad Abdalla Al-Zawi A, Syed A. Ki67 Proliferation index as a prognostic and predictive tool for pathological response after upfront chemotherapy in breast cancer. Paripex Indian Journal of Research. 2020; 9; 11.
2. Liang Q, Ma D, Gao RF, et al. Effect of Ki-67 Expression Levels and Histological Grade on Breast Cancer Early Relapse in Patients with Different Immunohistochemical-based Subtypes. Sci Rep. 2020; 10(1): 7648, doi: 10.1038/s41598-020-64523-1, indexed in Pubmed: 32376868.
3. Miller I, Min M, Yang C, et al. Ki67 is a Graded Rather than a Binary Marker of Proliferation versus Quiescence. Cell Rep. 2018; 24(5): 1105–1112.e5, doi: 10.1016/j.celrep.2018.06.110, indexed in Pubmed: 30067968.
4. Maranta AF, Broder S, Fritzsche C, et al. Do you know the Ki-67 index of your breast cancer patients? Knowledge of your institution's Ki-67 index distribution and its robustness is essential for decision-making in early breast cancer. Breast. 2020; 51: 120–126, doi: 10.1016/j.breast.2020.03.005, indexed in Pubmed: 32302928.
5. Soliman NA, Yussif SM. Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med. 2016; 13(4): 496–504, doi: 10.20892/j.issn.2095-3941.2016.0066, indexed in Pubmed: 28154782.
6. Bustreo S, Osella-Abate S, Cassoni P, et al. Optimal Ki67 cut-off for luminal breast cancer prognostic evaluation: a large case series study with a long-term follow-up. Breast Cancer Res Treat. 2016; 157(2): 363–371, doi: 10.1007/s10549-016-3817-9, indexed in Pubmed: 27155668.
7. Inic Z, Zegarac M, Inic M, et al. Difference between Luminal A and Luminal B Subtypes According to Ki-67, Tumor Size, and Progesterone Receptor Negativity Providing Prognostic Information. Clin Med Insights Oncol. 2014; 8: 107–111, doi: 10.4137/CMO.S18006, indexed in Pubmed: 25249766.
8. Prat A, Pascual T, Adamo B. Intrinsic molecular subtypes of HER2+ breast cancer. Oncotarget. 2017; 8(43): 73362–73363, doi: 10.18632/oncotarget.20629, indexed in Pubmed: 29088709.
9. Hashmi AA, Hashmi KA, Irfan M, et al. Ki67 index in intrinsic breast cancer subtypes and its association with prognostic parameters. BMC Res Notes. 2019; 12(1): 605, doi: 10.1186/s13104-019-4653-x, indexed in Pubmed: 31547858.
10. Kanyılmaz G, Yavuz BB, Aktan M, et al. Prognostic Importance of Ki-67 in Breast Cancer and Its Relationship with Other Prognostic Factors. Eur J Breast Health. 2019; 15(4): 256–261, doi: 10.5152/ejbh.2019.4778, indexed in Pubmed: 31620685.
11. Petric M, Martinez S, Acevedo F, et al. Correlation between Ki67 and histological grade in breast cancer patients treated with preoperative chemotherapy. Asian Pac J Cancer Prev. 2014; 15(23): 10277–10280, doi: 10.7314/apjcp.2014.15.23.10277, indexed in Pubmed: 25556461.
12. Al-Zawi A. Ki -67 proliferative index as a predictive tool for axillary pathological complete response in node-positive breast cancer. International Journal of Medical Science. 2020; 7(11): 1–4, doi: 10.14445/23939117/ijms-v7i11p101.

VIA MEDICA

ORIGINAL ARTICLE

Krzysztof Skowron[1], Ewa Wałecka-Zacharska[2], Natalia Wiktorczyk-Kapischke[1], Katarzyna Grudlewska-Buda[1], Zuzanna Bernaciak[1], Anna Gralewska[1], Eugenia Gospodarek-Komkowska[1]

[1]Department of Microbiology, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland
[2]Department of Food Hygiene and Consumer Health, Wrocław University of Environmental and Life Sciences, Wroclaw, Poland

Effect of *Lactobacillus spp.* strains on the population of *Listeria monocytogenes* isolated from the human vagina

Corresponding author:

Krzysztof Skowron, Department of Microbiology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, 9 M. Skłodowskiej-Curie Str., 85-094 Bydgoszcz, Poland; e-mail: skowron238@wp.pl

Medical Research Journal 2021; Volume 6, Number 1, 8–15
10.5603/MRJ.a2021.0001

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: The normal vaginal microbiota (mainly *Lactobacillus* spp.) affects the health of these areas. Bacterial vaginosis is a serious health problem among many women, especially dangerous for pregnant women. The study aimed to assess the impact of *Lactobacillus* spp. strains on the population of *Listeria monocytogenes* isolated from women.

Materials and methods: The research material consisted of reference strains of *Lactobacillus* spp.: *L. acidophilus* (LAC), *L. fermentum* (LFE), *L. gasseri* (LGA), *L. plantarum* (LPL), the strain *L. monocytogenes* ATCC 19111 and 7 *L. monocytogenes* strains isolated from the vagina.

Results: The highest antagonistic activity was shown for the mixed culture of all *Lactobacillus* strains (LACTO MIX) used in the experiment. Among the individual strains of *Lactobacillus* spp. strains, *L. plantarum* turned out to most effectively reduce *L. monocytogenes* number (reduction of 5.74 log CFU × ml^{-1}). The least effective in inhibiting the growth of *L. monocytogenes* was the *L. acidophilus* strain (reduction of *L. monocytogenes* of a number of 2.21 log CFU × ml^{-1}).

Conclusions: The presence of *Lactobacillus* spp. in the genital tract limits the development of bacterial infections, which is an important aspect especially for pregnant women.

Key words: *Lactobacillus* spp., *Listeria monocytogenes*, vaginal disease, probiotics, antagonistic action

Med Res J 2021; 6 (1): 8–15

Introduction

The microbiological profile of the vagina can form a stable ecosystem that contributes to maintaining vaginal health, preventing and eliminating the risk of infection. Disturbance of the right amount of bacterial microbiota promotes the development of bacterial vaginosis [1]. The condition of the vaginal microbiota depends on several factors, including age, health, eating habits, endocrine system and hygiene. The composition of the vaginal microbiome of women varies, depending on the part of the world [2–4]. Normal vaginal pH of premenopausal women may range from 3.5 to 4.5, as a result of the presence of different *Lactobacillus* spp. (10^7–10^8 CFU/g vaginal mucus in healthy premenopausal women), i.e. *L. crispatus*, *L. gasseri*, *L. jensenii*, *L. iners*, *L. acidophilus*, *L. fermentum*, *L. plantarum*, *L. brevis*, *L. casei*, *L. vaginalis*, *L. delbrueckii*, *L. salivarius*, *L. reuteri*, *L. rhamnosus* [5]. These bacteria are capable of producing lactic acid from glycogen and constitute from 80% to 95% of the vaginal microbiota of healthy women [6]. The vaginal vault is colonized within 24 hours of the birth of the girl, and the process continues until death [5]. Lactobacilli produce hydrogen peroxide, which limits vaginal colonization by catalase-negative bacteria and anaerobes. These products also affect the ability to adhere and compete for adhesion sites in the vagina with pathogenic microorganisms [1]. An important feature of the genus *Lactobacillus* is the synthesis of antimicrobials, which they can produce under aerobic and anaerobic conditions, such as peptides, bacteriocins and biosurfactants, which promote the xe-

nophagy (absorption and degradation by the host cells) of bacteria, viruses and protozoa. Thus, the positive role of lactobacilli is based on the inhibition of growth of other potentially pathogenic endogenous bacteria and prevention of the infection by exogenous bacteria. Therefore, the domination of *Lactobacillus* spp. in the vagina is essential for maintaining the women's health [7].

One of the most dangerous pathogens for pregnant women is *Listeria monocytogenes*. Pregnant women are 18 times more likely to be infected than in the general population [1]. While the maternal disease is usually mild, it can be severe and potentially fatal in newborn babies [5]. It is believed that about 5–10% of women are asymptomatic carriers of *L. monocytogenes* in the vagina and within the gastrointestinal tract [8]. An increase of the vaginal pH enables multiplication of *L. monocytogenes*, thereby posing a risk of the pathogen transmission from the mother to foetus/newborn via placental barrier or the birth canal [9]. Listeriosis most often occurs in the third trimester of pregnancy (from 28 weeks) and is rarely fatal for the mother, especially in the absence of concomitant diseases [10]. Symptoms of neonatal listeriosis include bacteraemia, respiratory failure, purulent conjunctivitis and skin lesions. The estimated incidence of pregnancy-related listeriosis ranges from 1 to 25 cases per 100 000 births, accounting for up to 35% of all *L. monocytogenes* infections [9]. The frequency of neonatal listeriosis is approximately 8.6/100 000 live births, with high mortality (20–60%) and is one of the most common causes of neonatal meningitis [9].

The study aimed to assess the impact of *Lactobacillus* spp. strains on the population of *L. monocytogenes* isolated from the female vagina.

Materials and methods

Bacterial strains

Four *Lactobacillus* spp. reference strains were used in the study: *L. acidophilus* ATCC 314 (LAC), *L. fermentum* ATCC 9338 (LFE), *L. gasseri* ATCC 19992 (LGA) and *L. plantarum* ATCC 8014 (LPL), the reference strain *L. monocytogenes* ATCC 19111 and 7 *L. monocytogenes* strains of serotype 1/2a-3a isolated from the vagina of healthy women. Clinical strains used in the study come from the collection of the Department of Microbiology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland.

Assessment of the number of *Lactobacillus spp.* in cultures without *L. monocytogenes* and in mixed cultures with *L. monocytogenes* strains

Lactobacillus spp. strains were plated on Rogosa Agar (Merck) and incubated at 35°C (72 h, microaerophilic conditions). For each strain, 10 suspensions of single colonies in LAPTg medium (5 ml of 0.5 McF) were prepared (medium composition: Pepton Tryptone 10 g/l, yeast extract 10 g/l, Pepton 15 g/l, glucose 10 g/l, Tween 80 1 ml/l) (Merck). *L. monocytogenes* strains were plated on Columbia Agar medium with 5% sheep blood (BioMerieux). After 24 h at 37°C single colonies were used to make suspensions in LAPTg medium (5 ml of 0.5 McF). Then mixed cultures were prepared with the following composition: LAC + LMO (each tested strain separately), LFE + LMO (each tested strain separately), LGA + LMO (each tested strain separately) and LPL + LMO (each tested strain separately) and mix of all tested *Lactobacillus* spp. strains (LACTO MIX). The volume of each bacterial suspension was 5 ml. The negative control consisted of mixtures: the reference strain *Lactobacillus* spp. + 5 ml of sterile LAPTg medium, the mixture of reference strains of *Lactobacillus* spp. + 5 ml of sterile LAPTg medium and the given *L. monocytogenes* strain + 5 ml of sterile LAPTg medium.

The prepared mixtures were incubated at 37°C for up to 72 hours. The number of *Lactobacillus* spp. and *L. monocytogenes* in mixed cultures was assessed after 0, 24, 48 hours of incubation. 10-fold serial dilutions in PBS were made and 100 μl was plated onto Rogosa Agar (Merck) for *Lactobacillus* and OXFORD agar (Oxoid) for *L. monocytogenes*. Cultures were incubated under microaerophilic (*Lactobacillus* spp.) and aerobic (*L. monocytogenes*) conditions at 35°C for 3 days and 48 hours at 37°C, respectively. The number of colonies was expressed as CFU $\times$ ml^{-1}.

To determine the ability of *Lactobacillus* spp. to multiply (with and without *L. monocytogenes)* during the experiment, the multiplication factor (F) was calculated according to the formula:

$$F = a/b, \text{ where:}$$

F – the multiplication factor; a – the initial number of *Lactobacillus* spp. bacteria after mixtures preparation [log CFU$\times$ml^{-1}]; b – the number of *Lactobacillus* spp. bacteria after 48-hour incubation [log CFU$\times$ml^{-1}].

Lactobacillus spp. antagonism in aerobic conditions against *L. monocytogenes*

The lawn plates on Rogosa Agar (Merck) were made for all reference strains of *Lactobacillus* spp. and their mix. After 24 h (35°C, microaerophilic atmosphere) agar discs with the grown colonies of *Lactobacillus* spp. (LAC, LFE, LGA, LPL and LACTO MIX) were cut with the sterile cork borer.

For each of the tested *L. monocytogenes* strains, a suspension of 0.5 McF in PBS (Avantor) was prepared and spread evenly on Columbia Agar with 5% sheep blood (bioMérieux). Next, agar discs of *Lactobacillus* spp. culture was placed on such a plate. The negative control were plates with sterile agar discs. Plates were incubated 48 h (aerobic conditions) at 37°C and growth inhibition zones around the agar discs were measured [diameter in mm]. The experiment was carried out in triplicate.

Suspensions of 10 μl of *Lactobacillus* spp. (0.5 McF) in PBS (Avantor) were plated onto Rogosa Agar (Merck) and were incubated (microaerophilic conditions, 37°C, 24 h). Then chloroform (Sigma-Aldrich) soaked sterile gauze pad was placed in a closed plate with *Lactobacillus* spp. culture for 20 min to kill microbes. The gauze was then removed and the plates were left in a sterile laminar chamber to allow chloroform evaporation (30 min.). *Lactobacillus* spp. colonies were removed from the plates with a sterile cotton swab. The plates were then covered with tempered BHI (Brain Heart Infusion) Agar (bioMérieux) containing the suspension (1 McF) of *L. monocytogenes* culture (250 μl of the suspension to 12 ml of agar). The negative control was *L. monocytogenes* culture on Rogosa Agar (Merck). After incubation, the zones of inhibition of *L. monocytogenes* growth were measured and expressed in millimetres [mm].

Statistical analysis

The statistical analysis was performed using the STATISTICA 13.0 PL program (StatSoft). The significant differences of bacteria number between different experimental conditions were checked with a one-way analysis of variance and a non-parametric Bonferroni posthoc test at significance level $\alpha = 0.05$.

The significant differences of inhibition zone of *L. monocytogenes* growth between *Lactobacillus* spp. strains were calculated with a one-way analysis of variance and the Tukey posthoc test at significance level $\alpha = 0.05$. To check significant differences of inhibition zone of *L. monocytogenes* growth, depending on the *Lactobacillus* spp. and *L. monocytogenes* strain, multiway analysis of variance and the Tukey posthoc test at significance level $\alpha = 0.05$ were applied.

Results

Assessment of *Lactobacillus spp.* number in cultures without *L. monocytogenes* and in mixed cultures with *L. monocytogenes* strains

We showed that the number of *Lactobacillus* spp. in the culture without *L. monocytogenes* and mixed culture increased together with the incubation time (Fig. 1A). The highest number of *Lactobacillus* spp. was observed in the LACTO MIX culture without *L. monocytogenes* (an increase of 9.79 log CFU × ml^{-1}, 48 h incubation). The slowest growth was demonstrated for the LGA strain with *L. monocytogenes* (increase by 5.40 log CFU × ml^{-1}, 24 h incubation). The increase of *Lactobacillus* spp. number, after 48 hours of *Lactobacillus* spp. culture with *L. monocytogenes*, ranged from 7.55 log CFU × m^{-1} (24 h) to 8.80 log CFU × ml^{-1} (48 h). The best growth in the presence of *L. monocytogenes* showed LPL whereas the slowest growth rate was found for LGA (Fig. 1A). The multiplication factor calculated for the tested *Lactobacillus* spp. strains ranged from 1.29 (LPL suspension without LMO) to 1.65 (LACTO MIX without LMO) (Fig. 1B).

Assessment of *L. monocytogenes* number in the culture with and without *Lactobacillus spp.*

The initial number of *L. monocytogenes* was 10^6 CFU × ml^{-1} and increased during incubation to 10^8–10^9 CFU × ml^{-1}, depending on the tested strain. In the experimental variant without *Lactobacillus* spp. the increase of *L. monocytogenes* number ranged from 6.67 log CFU × ml^{-1} (0h) to 9.00 log CFU × ml^{-1} (48h) (Fig. 2A). Lactobacilli had the antagonistic effect on *L. monocytogenes*. Regardless of the *Lactobacillus* spp. species and the *L. monocytogenes* strain, a statistically significant decrease in the number of *L. monocytogenes* was observed after 24 and 48 hours of cultivation (Fig. 2A). The mean of *L. monocytogenes* number at the initial time point ranged from 6.67 log CFU × ml^{-1} to 7.37 log CFU × ml^{-1} (Fig. 2A). There were no statistically significant differences in the reduction of *L. monocytogenes* number between particular, single strains of *Lactobacillus* spp. used in the co-culture. The highest antagonistic activity against *L. monocytogenes* had LACTO MIX culture (reduction number of bacteria was 4.79 log CFU × ml^{-1} after 24h incubation and 1.82 log CFU × ml^{-1} after 48 h incubation) (Fig. 2A, B).

The number of *L. monocytogenes* in such culture was statistically significantly lower compared to the number of *L. monocytogenes* incubated with a single species of *Lactobacillus* spp. (Fig. 2A). The reduction of *L. monocytogenes* number ranged from 1.99 log CFU × ml^{-1} (LAC) to 5.95 log CFU × ml^{-1} (LACTO MIX). Among the individual *Lactobacillus* strains, LPL reduced *L. monocytogenes* number most efficiently, whereas the least effective was LAC (Fig. 2B). The average number of *L. monocytogenes* after 24-hour culture with *Lactobacillus* spp. was 4.18 log CFU × ml^{-1} and 2.23 log CFU × ml^{-1} for LMO 7 and LMO 4 strains, respectively (Fig. 2C).

Lactobacillus spp. antagonism in aerobic conditions against *L. monocytogenes*

The greatest efficacy against *L. monocytogenes* was demonstrated in the mixed culture with LACTO MIX. The diameter of *L. monocytogenes* growth inhibition zone around the agar disc with the mixed culture of *Lactobacillus* spp. was 18.38 mm and was statistically significantly higher compared to the size of the zones around the discs with the individual lactobacilli strains tested (Fig. 3A).

The most effective among the single cultures of the tested *Lactobacillus* spp. species was the LPL strain

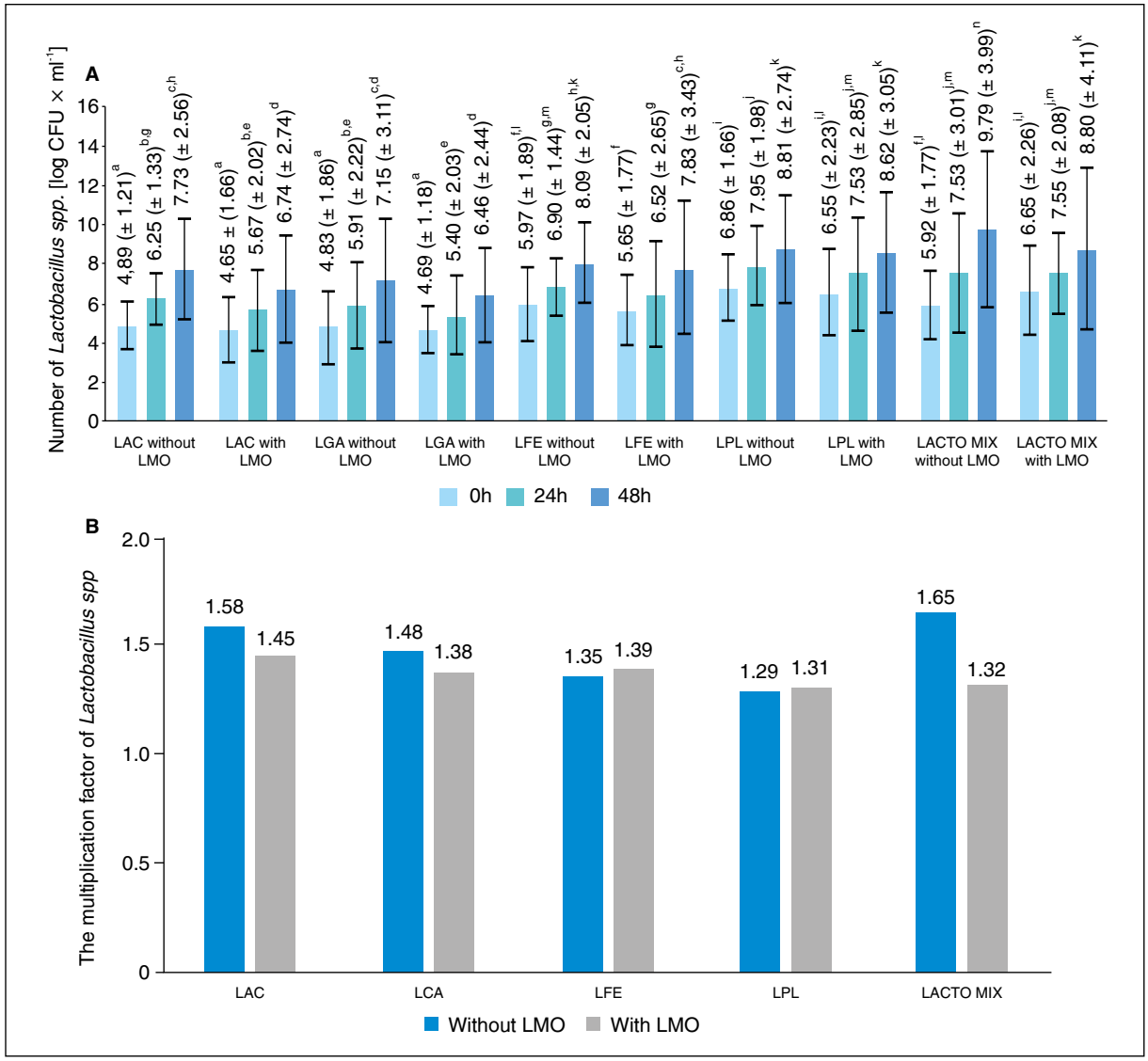


Figure 1. A. Changes in the number of *Lactobacillus* spp. in mixed culture with *L. monocytogenes*. **B.** The multiplication factor of *Lactobacillus* spp. LAC — *L. acidophilus* ATCC 314, LFE — *L. fermentum* ATCC 9338, LGA — *L. gasseri* ATCC 19992, LPL — *L. plantarum* ATCC 8014

(12.83 mm inhibition zone). The LAC strain was the least effective in controlling *L. monocytogenes* number (the average diameter of the inhibition zone of 8.50 mm). The obtained results showed that the antibacterial effectiveness of aerobic metabolites produced by *Lactobacillus* spp. depended on the tested *L. monocytogenes* strain (Fig. 3C). The most susceptible to aerobic metabolites of *Lactobacillus* spp., regardless of *Lactobacillus* species, was the LMO 4 strain (the average growth inhibition zone of 18.53 mm). The LMO 7 strain was the least sensitive to the aerobic metabolites of *Lactobacillus* spp. (the average growth inhibition zone of 6.80 mm) (Fig. 3C).

We showed that the LACTO MIX culture most effectively inhibited the growth of *L. monocytogenes*. The average diameter of the inhibition zone of the pathogenic bacteria growth on such plates was 11.67 mm and was statistically significantly bigger compared to the size of the zones on the plates with a single *Lactobacillus* spp. strain (Fig. 3B). Among individual cultures of the tested *Lactobacillus* spp. strains the highest efficacy against *L. monocytogenes* was found for LPL cultures (diameter of *L. monocytogenes* inhibition zone was 7.46 mm). The least effective in inhibiting the growth of *L. monocytogenes* was the LAC strain. The diameter of the growth inhibition zone was 4.75 mm and was

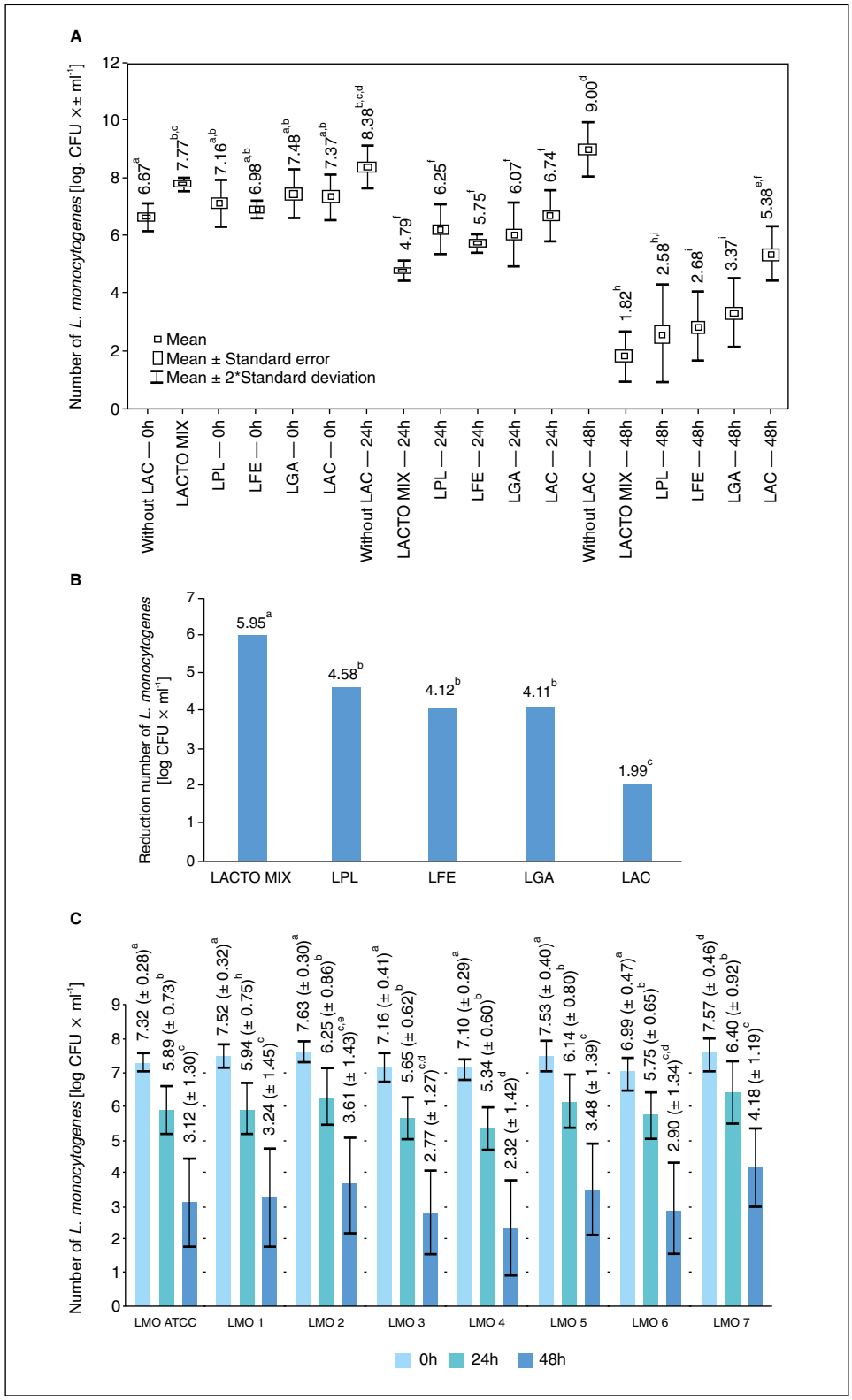


Figure 2. A. Changes in the number of *L. monocytogenes* in mixed culture with *Lactobacillus* spp. and without *Lactobacillus* spp. **B.** Decreases in *L. monocytogenes* number [log CFU × ml^{-1}] during 48 h of culture with *Lactobacillus* spp. Strains. **C.** Changes in the number of *L. monocytogenes* in the mixed culture with *Lactobacillus* spp. LAC — *L. acidophilus* ATCC 314, LFE — *L. fermentum* ATCC 9338, LGA — *L. gasseri* ATCC 19992, LPL — *L. plantarum* ATCC 8014; a,b,c,… — values marked with different letters differ statistically significant, *standard deviation, CFU — colony forming units

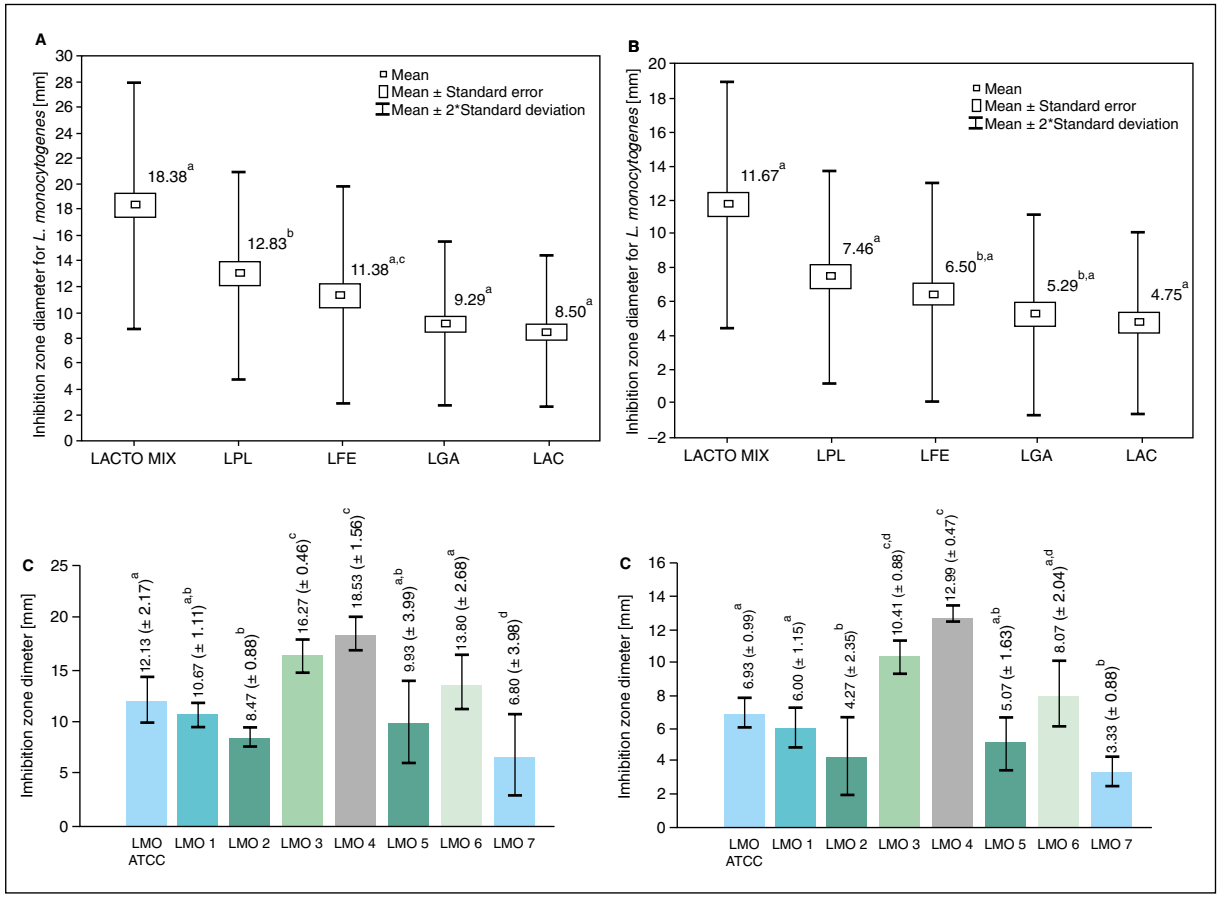


Figure 3. A. The effect of aerobic metabolites produced by *Lactobacillus* spp. strains on the size of growth inhibition zones of *L. monocytogenes*. **B.** The effect of anaerobic metabolites produced by *Lactobacillus* spp. strains on the size of growth inhibition zones of *L. monocytogenes*. **C.** The mean size of growth inhibition zones of *L. monocytogenes* due to the action of *Lactobacillus* spp. in aerobic condition. **D.** The mean size of growth inhibition zones of *L. monocytogenes* due to the action of *Lactobacillus* spp. in anaerobic conditions. LAC — *L. acidophilus* ATCC 314, LFE — *L. fermentum* ATCC 9338, LGA — *L. gasseri* ATCC 19992, LPL — *L. plantarum* ATCC 8014, a,b,c,… — values marked with different letters differ statistically significant, *standard deviation

statistically significantly smaller compared to the mixed LACTO MIX culture and the LPL culture (Fig. 3B).

It was shown that the sensitivity of *L. monocytogenes* to anaerobic metabolites of *Lactobacillus* spp. was strain-dependent (Fig. 3D). LMO4 strain was the most sensitive to bacteriocins, regardless of *Lactobacillus* species (the average inhibition zone of 12.99 mm). The LMO7 strain was the most resistant to *Lactobacillus* spp. in this variant of the experiment (the average inhibition zone of 3.33 mm) (Fig. 3D).

Discussion

The vagina of women is a natural habitat for many bacterial species, among which the predominant group are *Lactobacillus* spp. These bacteria, by secreting antimicrobial compounds, create a protective barrier against pathogenic microorganisms that cause urogenital infections [1]. One of the pathogens, dangerous especially for pregnant women, is *L. monocytogenes*. The available literature does not include studies assessing the effect of individual strains of *L. acidophilus, L. fermentum*, *L. gasseri*, *L. plantarum* and their mixture on the growth of pathogenic *L. monocytogenes*. So far, attention was paid mainly to the antagonistic properties of lactobacilli against such pathogens as *Streptococcus agalactiae*, *Gardnerella vaginalis*, and *Prevotella bivia*.

Our study showed that the mixed culture of *Lactobacillus* spp. has the highest antagonistic activity against *L. monocytogenes*. This supports the thesis that the best elimination of pathogenic microorganisms is guaranteed by the use of the culture of several *Lactobacillus* spp. strains, appropriately selected for a given female population [2, 11, 12]. Among the individual tested *Lactobacillus* spp. strains the most

effective in reducing *L. monocytogenes* number was *L. plantarum*, while the smallest activity had *L. acidophilus*. Bodaszewska-Lubas et al. [13] evaluated the effect of antimicrobial properties of *L. lactis, L. plantarum* and *L. sakei* against *S. agalactiae*. They also observed that *L. plantarum* was the most effective in controlling the pathogen number, while *L. lactis* slightly inhibited the growth of *S. agalactiae*, and *L. sakei* did not exhibit antagonistic properties against the tested bacterium [13]. In turn, Atassi et al. [11] studying the effect of *L. acidophilus, L. crispatus, L. gasseri* and *L. jensenii* on the female genital tract pathogens: *G. vaginalis* and *P. bivia* found that *L. gasseri* was the most effective. In the presented study, this species displayed a moderate antagonistic activity. The effect of *Lactobacillus* spp. on other pathogens, i.e. *Staphylococcus aureus*, *S. epidermidis*, *S. saprophyticus*, *S. agalactiae, Escherichia coli*, *L. monocytogenes, Candida* spp. was also described [2, 12, 14]. Also, Matu et al. [15] showed the inhibitory effect of *Lactobacillus* spp. on the pathogenic bacteria *P. bivia*, *G. vaginalis* and *Mobiluncus* spp. The inhibition of the growth of pathogenic microorganisms correlated with the production of organic acids such as lactic acid, hydrogen peroxide and bacteriocins by *Lactobacillus* spp strains. The growth inhibition zones were 1.5–8.0 mm for *G. vaginalis*, 1.0 - 8.0 mm for *Mobiluncus* spp. and 1.5–7.0 mm for *P. bivia*. They also demonstrated that *L. acidophilus* strain was the most effective in controlling pathogenic microorganisms [15]. In this study, the most effective among the single cultures of the tested *Lactobacillus* spp. species was the LPL strain (12.83 mm inhibition zone). Sabia et al. [16] showed that *L. fermentum* CS57 secreted a bacteriocin-like substance (BLS) with antagonistic activity against *S. agalactiae* and *Candida albicans*. In turn, Dembélé et al. [17] showed that mainly lactic acid is responsible for inhibiting the growth of pathogenic microorganisms and to a lesser extent bacteriocins secreted by *Lactobacillus* spp. strains. They also showed that the antimicrobial activity of *Lactobacillus* spp. against *L. monocytogenes* was lower compared to *S. aureus* and *Enterobacteriaceae*. The inhibition zone of *L. monocytogenes* growth ranged from 1.0 mm to 15.0 mm [17]. Gil et al. [12] showed that *L. salivarius* was the best producer of lactic acid. In turn, the study of Hütt et al. [18] found that the most efficiently lactic acid was produced by *L. gasseri*, followed by *L. crispatus* and *L. jensenii*. In the presented study, it was observed that both aerobic metabolites and bacteriocins secreted by *Lactobacillus* spp. strains inhibited *L. monocytogenes*. However, *Lactobacillus* spp. antagonism was higher under aerobic than anaerobic conditions. The sensitivity of *L. monocytogenes* in anaerobic conditions was strain-dependent. The susceptibility of tested strains to metabolites of *Lactobacillus* spp. was varied. In the available literature, no works that would unambiguously explain this phenomenon have been found. Therefore, more research is needed in this area. The resistance to antimicrobials can be inherent or acquired (e.g. in response to stress exposure). The resistance of *L. monocytogenes* strains to antibacterial metabolites of *Lactobacillus* spp. can be associated with a decreased expression of Man-PTS genes (Mannose Phosphotransferase System), responsible for the import and phosphorylation of sugars such as glucose and mannose. It has been speculated that the changes in gene expression result from the process leading to metabolic variability rather than a spontaneous mutation [19]. The role of *anrB* (encoding the permease component of an ABC transporter), *lmo222* (encoding the penicillin-binding protein) and *dltA (*responsible for the cell wall synthesis) genes in the tolerance of *L. monocytogenes* to bacteriocins has also been reported [20].

Conclusions

Lactobacillus spp. plays a key role in controlling the growth of pathogenic *L. monocytogenes* in the woman's vagina. The best results give the application of the mixed culture of a few strains. Nonetheless, there is a need for further research to accurately determine the concentration of *Lactobacillus* spp. metabolites and to understand the mechanism of their action on pathogenic bacteria, including *L. monocytogenes.*

Funding source: *This research was funded by the Nicolaus Copernicus University with funds from the maintenance of the research potential of the Department of Microbiology PDB WF 536.*

Conflict of interest: *The authors declare that they have no conflict of interest.*

References

1. Borges S, Silva J, Teixeira P. The role of lactobacilli and probiotics in maintaining vaginal health. Arch Gynecol Obstet. 2014; 289(3): 479–489, doi: 10.1007/s00404-013-3064-9, indexed in Pubmed: 24170161.
2. Eslami G, Karimiravesh R, Taheri S, et al. Inhibitory Effect of Lactobacillus reuteri on Some Pathogenic Bacteria Isolated From Women With Bacterial Vaginosis. Avicenna Journal of Clinical Microbiology and Infection. 2014; 1(2): 19908–19908, doi: 10.17795/ajcmi-19908.
3. Strus M. Podstawy stosowania probiotyków dopochwowych w zakażeniach narządu moczowo-płciowego. Zakażenia. 2005; 4: 40–43.
4. Strus M, Malinowska M. Zakres antagonistycznego działania bakterii z rodzaju Lactobacillus na czynniki etiologiczne waginozy bakteryjnej. Med Dośw Mikrobiol. 1999; 51: 47–57.
5. Farage M, Miller K, Sobel J. Dynamics of the Vaginal Ecosystem—Hormonal Influences. Infectious Diseases: Research and Treatment. 2010; 3: IDRT.S3903, doi: 10.4137/idrt.s3903.
6. Cribby S, Taylor M, Reid G. Vaginal microbiota and the use of probiotics. Interdiscip Perspect Infect Dis. 2008; 2008: 256490, doi: 10.1155/2008/256490, indexed in Pubmed: 19343185.

7. Amabebe E, Anumba DOC. The Vaginal Microenvironment: The Physiologic Role of . Front Med (Lausanne). 2018; 5: 181, doi: 10.3389/fmed.2018.00181, indexed in Pubmed: 29951482.
8. Jurkiewicz A, Oleszczak-Momot W. Listeria monocytogenes jako problem zdrowia publicznego. Medycyna Ogólna i Nauki o Zdrowiu. 2015; 21(1): 29–32.
9. Madjunkov M, Chaudhry S, Ito S. Listeriosis during pregnancy. Arch Gynecol Obstet. 2017; 296(2): 143–152, doi: 10.1007/s00404-017-4401-1, indexed in Pubmed: 28536811.
10. Jin L, Tao L, Pavlova SI, et al. Species diversity and relative abundance of vaginal lactic acid bacteria from women in Uganda and Korea. J Appl Microbiol. 2007; 102(4): 1107–1115, doi: 10.1111/j.1365-2672.2006.03147.x, indexed in Pubmed: 17381754.
11. Atassi F, Brassart D, Grob P, et al. Lactobacillus strains isolated from the vaginal microbiota of healthy women inhibit Prevotella bivia and Gardnerella vaginalis in coculture and cell culture. FEMS Immunol Med Microbiol. 2006; 48(3): 424–432, doi: 10.1111/j.1574-695X.2006.00162.x, indexed in Pubmed: 17059467.
12. Gil NF, Martinez RCR, Gomes BC, et al. Vaginal lactobacilli as potential probiotics against Candida SPP. Braz J Microbiol. 2010; 41(1): 6–14, doi: 10.1590/S1517-83822010000100002, indexed in Pubmed: 24031455.
13. Bodaszewska-Lubas M, Brzychczy-Wloch M, Gosiewski T, et al. Antibacterial activity of selected standard strains of lactic acid bacteria producing bacteriocins--pilot study. Postepy Hig Med Dosw (Online). 2012; 66: 787–794, doi: 10.5604/17322693.1015531, indexed in Pubmed: 23175332.
14. Stoyancheva G, Marzotto M, Dellaglio F, et al. Bacteriocin production and gene sequencing analysis from vaginal Lactobacillus strains. Arch Microbiol. 2014; 196(9): 645–653, doi: 10.1007/s00203-014-1003-1, indexed in Pubmed: 24919535.
15. Matu MN, Orinda GO, Njagi ENM, et al. In vitro inhibitory activity of human vaginal lactobacilli against pathogenic bacteria associated with bacterial vaginosis in Kenyan women. Anaerobe. 2010; 16(3): 210–215, doi: 10.1016/j.anaerobe.2009.11.002, indexed in Pubmed: 19925874.
16. Sabia C, Anacarso I, Bergonzini A, et al. Detection and partial characterization of a bacteriocin-like substance produced by Lactobacillus fermentum CS57 isolated from human vaginal secretions. Anaerobe. 2014; 26: 41–45, doi: 10.1016/j.anaerobe.2014.01.004, indexed in Pubmed: 24462825.
17. Dembélé T, Obdrzálek V, Votava M. Inhibition of bacterial pathogens by lactobacilli. Zentralbl Bakteriol. 1998; 288(3): 395–401, doi: 10.1016/s0934-8840(98)80013-3, indexed in Pubmed: 9861683.
18. Hütt P, Lapp E, Štšepetova J, et al. Characterisation of probiotic properties in human vaginal lactobacilli strains. Microb Ecol Health Dis. 2016; 27: 30484, doi: 10.3402/mehd.v27.30484, indexed in Pubmed: 27527701.
19. Kjos M, Nes IF, Diep DB. Mechanisms of resistance to bacteriocins targeting the mannose phosphotransferase system. Appl Environ Microbiol. 2011; 77(10): 3335–3342, doi: 10.1128/AEM.02602-10, indexed in Pubmed: 21421780.
20. Kaur G, Malik RK, Mishra SK, et al. Nisin and class IIa bacteriocin resistance among Listeria and other foodborne pathogens and spoilage bacteria. Microb Drug Resist. 2011; 17(2): 197–205, doi: 10.1089/mdr.2010.0054, indexed in Pubmed: 21417775.

VIA MEDICA

ORIGINAL ARTICLE

Sedighe Samimian[1], Tahereh Khaleghdoost[2], Ali Ashraf[1], Hamideh Hakimi[3]

[1]Clinical Research Development Unit of Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
[2]Instructor of Medical-Surgical Nursing Department of Nursing, School of Nursing and Midwifery Guilan University of Medical Sciences, Iran
[3]Student in Nursing, Department of Nursing, Lahijan Branch, Islamic Azad University, Lahijan, Iran

Effect of body mass index on intra-abdominal pressure in patients hospitalized in ICUs

Corresponding author:

Tahereh Khaleghdoost, Instructor of Medical-Surgical Nursing Department of Nursing, School of Nursing and Midwifery Guilan University of Medical Sciences, Iran,
e-mail: crdu_poursina@gums.ac.ir

Medical Research Journal 2021; Volume 6, Number 1, 16–20
10.5603/MRJ.a2021.0044

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Results: Considering the prevalence of obesity, overweight and risk factors related to the patients with Intra-abdominal pressure, the body mass index is among the factor which should be highly focused on these patients. The main objective of this study was to evaluate the effect of body mass index on Intra-abdominal pressure in patients hospitalized in ICUs.

Material and methods: The present research is a prospective, nonexperimental study conducted on 76 patients hospitalized in ICUs. Measurements of Intra-abdominal pressure were carried out based on the modified Korn method every day with 8-hour intervals. The instrument used for this purpose is a questionnaire consisting of three parts including demographic information, Sequential Organ Failure Assessment (SOFA) score, and intra-abdominal pressure monitoring form and record of its related parameters.

Results: The mean body mass index (BMI) scores revealed that 27.60% of the patients suffer from overweight and 7.2% of them have obesity problems with Intra-abdominal pressure of 8.44 ± 4.02 mmHg. For 15.8% and 2.6% of samples, Intra-abdominal hypertension of types I and II were observed, respectively. No sample was detected within the abdominal compartment. The average Intra-abdominal pressure for different BMIs indicated a statistically significant difference ($p = 0.007$), whereby an increase in BMI, IAP also indicates an increase.

Conclusion: The present research indicated no obesity evidence so that no relation was observed between IAP and obesity.

Key words: body mass index, intra-abdominal pressure, ICU

Med Res J 2021; 6 (1): 16–20

Introduction

The abdomen is an enclosed space surrounded by different hard walls such as spines, pelvis, and ribs as well as soft walls such as abdomen wall, Viscera, and diaphragm that serves as a Liquid environment, so that, Intra-abdominal pressure (IAP) functioning is based on Pascal's Hydrostatic Laws [1]. According to this law, the IAP might be associated with individual anatomic characteristics such as body size, muscle tone or abdominal problems such as ascites, peritonitis, hemoperitoneum, and trauma [2]. Moreover, variations of IAP are related to Body Mass Index (BMI), obesity, and dynamics of the chest and abdomen. The normal IAP in healthy adults and critically ill patient adults is 0 to 5 and 5 to 7mmHg, respectively [1, 3, 4], while it is reported as 7 to 14 mmHg for people with obesity [1, 3].

The studies show that BMI is responsible for 25 to 36% of IAP variations in critically ill patients [5]. Obesity is the direct responsibility of 300,000 annual death and a cost exceeding 100 billion dollars every year [6]. Recent studies have confirmed that prevalence and spread of Intra-Abdominal Hypertension (IAH) and abdominal compartment syndrome is associated with organ failure and mortality increase risks [7–9]. Based on previous studies, IAH in critically ill patients has been reported a range of 18 to 58.8%. It must be noted that this wide range is related to different clinical (surgical or medical) environments, different measurement techniques, and different definitions and scales of IAH [1, 7, 10]. The World Society of the Abdominal Compartment Syndrome introduces BMI greater than 30 kg/m^2 or obesity among the risk factors of IAH [11]. Moreover, the prevalence of obesity in medical and surgical ICUs

is reported up to 25% [12]. ICU patients have various IAH factors due to their particular conditions. Hence, due to the increasing rate of obesity and having other factors of IAH risk in this group of patients, it is highly recommended to pay special attention to BMI as one of IAH risk factors.

Assessment and measurement of IAP, similar to other hemodynamic parameters, are among the tasks of ICU nurses. Nurses should be particularly aware of IAP monitoring processes and their different aspects, as achieving these skills is necessary for the prognosis of patients exposed to the risk of IAH. By learning these skills, it is possible to reduce IAP and prevent the occurrence of ACS.

As previously mentioned, BMI is in close relation with IAP, and obese people are typically expected to have higher IAP. However, no study shows the effect of different BMI groups on IAP [13]. Considering the importance of IAH and attention of nurses to critical patients, this study was conducted to investigate the relationship between different BMI groups and other variables associated with IAP in ICU patients.

Material and methods

This analytical-sectional study was conducted to study the relationship between IAP and BMI in ICU patients. After obtaining a permit of the Ethics Committee of Guilan University of Medical Sciences, this research was conducted on 76 ICU patients hospitalized in educational health centres of Rasht. The criteria to enter this study are having age above 18 years, hospitalization in ICU and Ventilation with a ventilator for at least 24 hours, having Foley catheter and nasogastric tube, and Richmond agitation and sedation scores of -5 and -4, respectively, lack of spine damage, and high ICP. Moreover, among the criteria to leave the research are intolerance to the recumbent position for measuring IAP as the homodynamic variations and respiratory distress.

The instrument applied in this research is extracted from the World Society of the Abdominal Compartment Syndrome which consists of three parts. Demographic information (age, gender, BMI, and disease prognosis index), Sequential Organ Failure Assessment (SOFA) score, and IAP monitoring and record of its related parameters (i.e., average artery pressure, mean airway pressure, maximum airway pressure, plateau pressure, positive airway pressure, and mode of ventilator machine).

The sampling process was performed from Nov 6^{th,} 2011 to Feb 4^{th,} 2012, for three months from ICUs of hospitals related to Guilan University of Medical Sciences. Among the 289 patients visited in ICU, 76 qualified patients entered the study after obtaining informed consent from their legal custodian. The measurement procedure for each trial (24 hours with 8-hour intervals), based on modified Korn method, was as: After selecting the given sample, Under sterile conditions a bottle with infusion liquid (sterilized NaCl 0.9%, 500 ml) connected with a three-way connector, One side is connected to a full catheter introduced transurethrally into the bladder and another side is connected to water monometer.

The patient was placed in a supine position. After marking the patient's skin in the crest iliac area on the mid-auxiliary line (for preventing changes in the following measurements), the zero point of water monument was adjusted with the marked area, then clumping the tube of urine bag, in the nearest place to the Foley probe of the patient and 25 ml of sterilized saline normal solution with body temperature gently into the bladder. To create a balance between a patient's body after injecting normal saline solution and adjusting the patients at a head-of-bed angle, IAP and other pressure parameters were measured 60 sec later. After 30 sec, the junction attached to the Foley probe was opened towards the water monometer and the IAP was recorded at end-expiratory after some respirations.

After IAP measurement was done, the clump is removed and the corresponding nurse is reminded to make sure the volume of normal saline injected into the bladder is less than the volume of urine output of the patient. Using the overhead monitoring system, the mean artery pressure of the patients were measured and recorded. Each IAP measurement took 7 to 8 minutes. During the IAP measurements, in the case of IAH, the nurse and physician were informed about it to do required treatment measures. To measure BMI, height, and weight of patients, the information recorded in their medical file was used. Also, BMI categorization and measurement was carried out using the WHO classification (2000), where BMI < 18.5 kg/m^2: less than normal weight, 18.50 kg/m2 to 24.99 kg/m2: normal, 25 to 29.99 kg/m^2: overweight, and BMI > 30 kg/m^2: obesity.

Statistical methods

The obtained data were analyzed using descriptive and inferential statistics. Kolmogorov-Smirnov test was used to assess the normality of data. One-way ANOVA and the trend test were used to determine the significances of age, sex, and operative time differences between the three groups, and one-way ANOVA was used to assess intergroup differences concerning the relationship between IAP

ANOVA tests, using Bonferroni Post hoc, Pearson correlation coefficient using SPSS version 20 was used for data analysis. Statistical significance was accepted for p values of < 0.05.

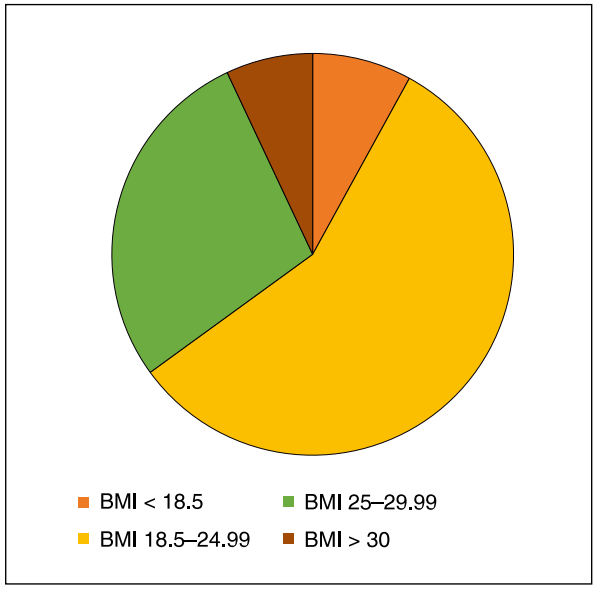


Figure 1. Distribution of participants according to BMI groups

Results

Based on the criteria for entering the research, 76 ICU patients selected from Rasht (Northern Iran) were studied in this research. The average age of patients was 50.31years, while their mean BMI score was 23.7. Besides, 27.6%, 7.2%, and 57% of the samples had overweight, obesity, natural weight, respectively; (Fig. 1) 60.5% of the samples were detected with trauma; 89.5% were under SIMV mode ventilation; the average hospitalization age was 5.43 days (Tab. 1). Based on the results of this research, the mean IAP within 24 hours was 8.44 ± 4.02 62 (81.58%) patients had normal IAP; (15.8%) patients had IAH type I, and 2 (2.6%) of them suffered from IAH type II. It must be noted that no patient had abdomen compartment syndrome.

Furthermore, there was found a significant relationship between IAP with SOFA score ($P < 0.01$) and hospitalization length ($P < 0.01$) and IAP with mean airway pressure, plateau pressure, positive end-expiratory pressure, and mean artery pressure ($P < 0.01$). Also, a significant relationship was found between IAP and age ($P < 0.01$) and prognosis ($P < 0.04$), as the mean IAH was higher for patients with internal problems as compared to those suffering from trauma. Finally, there was not a significant relationship between mean IAP and gender and mode of the ventilator system. The results also showed that average IAP indicates a statistically significant difference ($P = 0.007$) for at different BMI levels and mean IAP rises with the increasing BMI (Tab. 2).

Body mass index as a risk factor for intra-abdominal hypertension by Post Hoc Bonferroni test was further evaluated. It was shown that the average intra-abdominal pressure in obese (BMI > 30 kg/m^2) compared with overweight (25–29.99 kg/m^2) was significant. ($P < 0.009$) and also between obese subjects with normal BMI seen. ($P < 0.021$) (Tab. 3).

Table 1. Demographic and clinical characteristics of study population

Variable	Mean and standard deviation
Patient demographics	
age [y]	50.31 ± 20.47
BMI [kg/m^2]	23.70 ± 6.94
sex	
Male	55[72.4%]
Female	21[27.6%]
Clinical characteristics	
Diagnosis	
Trauma	46[60.5%]
Medical	30[39.47%]
Mechanical ventilation	
SIMV	68[89.5%]
BIPAP	2[2.6%]
CPAP	6[7.9%]
Length of stay [day]	5.43 ± 5.1
SOFA	6.85 ± 3.07
MAP [mmHg]	95.15 ± 17.66
PIP [cmH_2o]	26.59 ± 6.93
Plateau pressure [cmH_2o]	17.05 ± 5.53
Mean air way pressure [cmH_2o]	9.67 ± 2.4
APP [mmHg]	86.71 ± 1.65
IAP [mmHg]	8.44 ± 4.02

BMI — Body mass index
SIMV — Synchronized intermittent mandatory ventilation
BIPAP — Bi-level positive airway pressure
CPAP — Continuous positive airway pressure
SOFA — Sequential Organ Failure Assessment
MAP — Mean arterial pressure
PIP — Peak inspiratory pressure
APP — Abdominal perfusion pressure
IAP — Intra-abdominal pressure

Discussion and conclusion

The results of this research showed that there is a statistically significant relationship between age and IAP, as by an increase in age, also IAP score rises. Murcia-Sáez et al (2010) also found a significant relationship between the ages and mean IAP in their research units

[13]. This relationship was also significant in the work done by Ejika et al (2010) on patients younger than 18 years [14]. Considering the increased incidence of different chronic and internal diseases by age, IAP increase is also probable in the patients. However, the work conducted by Vasquez et al (2007) does not show such a significant relationship between age and IAP [5].

Table 2. Analysis of variables related to IAP

Variable	Mean and standard deviation of IAP	Sig.
Age (year)		< 0.001
18–35	99.2 ± 36.6	
36–65	17.4 ± 23.9	
> 66	08.4 ± 68.9	
Gender		0.15
Male	93.3 ± 16.8	
Female	24.4 ± 17.9	
Body mass index (BMI)		0.007
< 18.5	23.2 ± 84.10	
18.5–24.99	10.4 ± 04.8	
25–29.99	50.3 ± 16.7	
> 30	13.3 ± 62.12	
Prognosis		0.004
Traumatic	78.3 ± 6.7	
Medical	15.4 ± 67.9	
Mode of ventilator system		0.64
SIMV	22.4 ± 36.8	
BIPAP	95.0 ± 02.8	
CPAP	77.1 ± 51.9	

In the matters of the relation between IAP and prognosis, it was shown that the mean IAP of the patients with trauma is less as compared to the patients with internal diseases (i.e., 7.6 ± 3.78 mmHg versus 9.67 ± 4.15 mmHg), which is statistically significant. Based on the work conducted by McBeth et al (2007), the relation between IAP and prognosis of neurological illness is significant. In comparison, this relationship is not significant for surgical and traumatic patients [15]. In the study done by Malbrain et al (2004), no significant relation was found between prognosis of internal disease and traumatic diseases with IAP [2]. Likewise, the research conducted by Ejik et al (2010) on patients younger than 18 years indicated no relation between prognosis and IAP variations [14].

Based on the results of this research, no significant relation is observed between mean IAP score and SOFA score, hospitalization length, average airway pressure, plateau pressure, end-expiratory positive pressure, and mean artery pressure. The study conducted by Krebs et al (2009), "Effects of positive end-expiratory pressure on respiratory function and hemodynamics in patients with acute respiratory failure with and without intra-abdominal hypertension", indicated the presence of no statistically significant relation between plateau pressure and IAP [16].

Based on the results of this work, there is a significant relation between IAP and BMI. Vasquez et al (2007) reported a statistically significant relationship between

Table 3. Comparison of mean differences of IAP between BMI groups

BMI	Comparison groups	The mean difference of IAP	Standard Error	CI 95%	Sig. (Bonferroni method)
BMI < 18.50	Normal	2.69	1.75	-2.05, 7.44	0.76
	Overweight	3.50	1.85	-1.53, 8.53	0.37
	Obesity	-2.24	2.23	-8.30, 3.80	0.1
18.50–24.99	Less than normal weight	-2.69	1.75	-7.44, 2.05	0.76
	Overweight	0.80	1.07	-2.09, 3.71	0.1
	Obesity	-4.94	1.63	-9.38, -0.50	0.02
25.00–29.99	Less than normal weight	-3.50	1.85	-8.53, 1.53	0.37
	Normal	-0.80	1.07	-3.71, 2.09	0.1
	Obesity	-5.75	1.75	-10.50, -1.00	0.009
BMI > 30.00	Less than normal weight	2.24	2.23	-3.80, 8.30	0.1
	Normal	4.94	1.63	0.50, 9.38	0.1
	Overweight	5.75	1.75	1.00, 10.5	0.009

BMI and mean IAP and found that BMI is responsible for 25-36% of IAP variations [5]. Furthermore, McBeth et al found a significant relationship between BMI and IAP. Cobb et al (2005) reported that IAP is related to BMI in healthy adults [17]. In another research, Rein tam et al (2008) found that patients suffering from IAH have higher BMI scores as compared to patients without IAH and BMI is detected as an independent risk factor for IAP increase [7]. On the other hand, the work performed by Malbrain (2000) indicated no significant relationship between high IAP and BMI [18]. Similarly, the study done by Vasquez et al (2007) on the study of BMI effect on IAP by comparing different BMI groups indicated that IAP does not have a significant difference in various BMI groups [5].

The present research indicated no obesity evidence so that no relation was observed between IAP and obesity. The previous researches, however, showed the chronic increase of IAP in patients with obesity [19].

It seems that the higher fat content around the abdominal cavity (central obesity) in people with higher BMI results in the increased IAP by direct impact on the abdominal cavity and pelvis bottom [3]. Considering the factors effective on IAP such as intestine compaction by the increase in BMI induced by the fats around the abdominal area, it is expected that the increase in BMI results in increased IAP.

Among the limitations of this research are lack of conducting work on the relationship between sagittal abdominal diameter (SAD) and IAP. The relationship between IAP and BMI might be majorly related to the central obesity of the abdominal area. For further works, it is suggested to organize a similar work in groups with BMI greater than 30 which involves people with obesity, as well as studying the relationship between IAP and SAD. Furthermore, it is recommended to use IAP as a part of the monitoring process in ICU and pay further attention to high BMI as an IAH risk factor.

Acknowledgement

We offer our gratitude to the research deputy of Guilan University of Medical Sciences for supplying the budget needed in this research, the members of research board, and staffs from ICU and educational units of Poursina Hospital, Rasht. This paper is extracted from special M.Sc. theses passed in research deputy of Guilan University of Medical Sciences with the registration number: N2010102147872.

References

1. Mabrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multi-center epidemiological study. Intensive Care Med. 2004; 30(5): 822–9.
2. Gallagher J. , Intra-abdominal Hypertension, AACN Advanced Critical Care. 2010; 21(2): 205–217.
3. De K, De W, Powell B, et al. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end –expiratory pressure? Intensive Care Med. 2009; 35: 969–976.
4. De Waele JJ, Cheatham ML, Malbrain ML, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. Intensive Care Med. 2006; 32(11): 1722–1732, doi: 10.1007/s00134-006-0349-5, indexed in Pubmed: 16967294.
5. Vasquez DG, Berg-Copas GM, Wetta-Hall R. Influence of semi--recumbent position on intra-abdominal pressure as measured by bladder pressure. J Surg Res. 2007; 139(2): 280–285, doi: 10.1016/j.jss.2006.10.023, indexed in Pubmed: 17161433.
6. Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. J Urol. 2009; 182(6 Suppl): S2–S7, doi: 10.1016/j.juro.2009.08.071, indexed in Pubmed: 19846133.
7. Yi M, Leng Y, Bai Yu, et al. The evaluation of the effect of body positioning on intra-abdominal pressure measurement and the effect of intra-abdominal pressure at different body positioning on organ function and prognosis in critically ill patients. J Crit Care. 2012; 27(2): 222.e1–222.e6, doi: 10.1016/j.jcrc.2011.08.010, indexed in Pubmed: 22033056.
8. Kimball EJ, Rollins MD, Mone MC, et al. Survey of intensive care physicians on the recognition and management of intra-abdominal hypertension and abdominal compartment syndrome. Crit Care Med. 2006; 34(9): 2340–2348, doi: 10.1097/01.CCM.0000233874.88032.1C, indexed in Pubmed: 16878034.
9. Rein ta, Parm P, Kern H, et al. Primary and secondary intra-abdominal hypertension different impact on ICU outcome. Intensive Care Med. 2008; 34: 1624.
10. Malbrain M, Chiumello D, Pelosi P, et al. Incidence and prognosis of intra-abdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005; 33: 315–322.
11. Santa-Teresa P, Muñoz J, Montero I, et al. Incidence and prognosis of intra-abdominal hypertension in critically ill medical patients: a prospective epidemiological study. Ann Intensive Care. 2012; 2 Suppl 1: S3, doi: 10.1186/2110-5820-2-S1-S3, indexed in Pubmed: 22873419.
12. Aaron J. Wood. , Obesity in critically care, current opinion Anesthesiology. 2007; 20(2): 113–8.
13. Murcia I, et al. Sobbing- Hernandez M., Garcia- lopes n. Usefulness of intra-abdominal pressure in a predominantly medical intensive care unit Journal of critical care. ; 2010: 25175e1–175e6.
14. Ejike JC, Kadry J, Bahjri K, et al. Semi-recumbent position and body mass percentiles: effects on intra-abdominal pressure measurements in critically ill children. Intensive Care Med. 2010; 36(2): 329–335, doi: 10.1007/s00134-009-1708-9, indexed in Pubmed: 19898835.
15. McBeth PB, Zygun DA, Widder S, et al. Effect of patient positioning on intra-abdominal pressure monitoring. Am J Surg. 2007; 193(5): 644–7; discussion 647, doi: 10.1016/j.amjsurg.2007.01.013, indexed in Pubmed: 17434374.
16. Krebs J, Pelosi P, Tsagogiorg C, et al. Effect of positive end-expiratory pressure on respiratory function and hemodynamics in patients with acute respiratory failure with and witnout intra-abdominal hypertension: a pilot study. crit care. 2009; 13(5): R160.
17. Cobb WS, Burns JM, Kercher KW, et al. Normal intraabdominal pressure in healthy adults. J Surg Res. 2005; 129(2): 231–235, doi: 10.1016/j.jss.2005.06.015, indexed in Pubmed: 16140336.
18. Malbrain M. Relationship of body mass index (BMI), lactate and intra--abdominal pressure (IAP) to subsequent mortality in ICU patients. Critical Care. 1999; 3(Suppl 1): P039, doi: 10.1186/cc414.
19. Hon I, WuK So, Hyup Na, et al. Hon I, WuK Son D, Hyup Nam K, Chio B, Sung Song G, The effect of body mass index on intra-abdominal pressure and blood loss in lumbar spine surgery, J Korean Neurosurg Soc. 2012; 51: 81–85.

VIA MEDICA

ORIGINAL ARTICLE

Piotr Michalski[1], Michał Kasprzak[2], Agata Kosobucka[1], Łukasz Pietrzykowski[1], Małgorzata Jasiewicz[2], Aldona Kubica[1]

[1]Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Department of Cardiology and Internal Diseases, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Sociodemographic and clinical determinants of the functioning of patients with coronary artery disease

Corresponding author:

Piotr Michalski, Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Lukasiewicza 1 Str., 85–821 Bydgoszcz, Poland, e-mail: michalski.piotr@onet.eu

Medical Research Journal 2021; Volume 6, Number 1, 21–27
10.5603/MRJ.a2021.0003

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: Chronic diseases affect many aspects of patients' lives in various ways, including physical activity, emotional and spiritual sphere as well as social functioning. The study aimed to identify factors that determine the functioning of people with CAD, based on the original self-reported questionnaire.

Material and methods: A single-centre, prospective, observational cohort study was carried out in 202 consecutive patients hospitalized due to CAD. The study assessed their functioning in chronic disease using the comprehensive tool: The Functioning in Chronic Illness Scale.

Results: Most of the respondents (44.55%) showed a medium level of functioning in CAD [79 < result < 94 points]. Economic status (average) was an independent factor contributing to better functioning in the disease. Treatment time (1–5 years), marital status (widow/widower) and prior PTCA treatment were independent risk factors for worse FCIS scores. The independent factors determining the negative impact of the disease on the patient were: previous invasive treatment (PTCA and/or CABG) and age (> 65 years), while the independent determinants of the belief that the course of the disease can be modified were: sex (male) and duration of the disease (< 1 year).

Conclusions: The study identifies independent factors affecting the functioning of patients with CAD. FCIS questionnaire comprehensively measures patients' beliefs about the disease. Effective assessment of the quality of the patient's functioning in the disease may be useful in more individualized therapeutic management.

Key words: coronary artery disease, functioning in the disease, chronic diseases

Med Res J 2021; 6 (1): 21–27

Introduction

CAD affects many aspects of patients' lives in many ways, including physical activity, emotional and spiritual spheres, or social functioning. Limited functioning of a patient with chronic disease results in decreased self-esteem, deteriorated well-being, increased anxiety and uncertainty about the future [1–4].

The studies available to date are lacking in a comprehensive, multi-faceted assessment of the impact of chronic diseases on patients global functioning. The FCIS questionnaire, validated in patients with CAD, is a unique tool in this respect, providing the possibility of a comprehensive assessment of functioning in chronic disease [5].

This study aimed to identify factors that determine the functioning of patients with CAD, with the use of the FCIS questionnaire.

Material and methods

The single-centre prospective observational study was planned by the principles of ethics of the Helsinki Declaration and was approved by the Bioethics Committee of L. Rydygier Collegium Medicum, Nicolaus Copernicus University in Torun, Poland (no. KB 769/2016). The study enrolled patients between September 2017 and March 2019 admitted to the Cardiology Department, University Hospital No. 1 in Bydgoszcz, who met the following criteria:

1. treated or/and diagnosed with CAD at least 6 months before the hospital admission;
2. age ≥ 18 years;
3. written informed consent to participate in the study;
4. ability to self-filling in the patient survey and FCIS questionnaire.

The patient survey inquires about their sociodemographic status (age, sex, place of residence, level of education, marital status), economic factors (a type of employment, economic status) and health (height and weight, family history of cardiovascular diseases, treatment duration of CAD, previous invasive procedures for cardiovascular disease, smoking habit).

The FCIS is a new self-reported questionnaire for patients with chronic disease assessing the impact of the disease on the patient, the patient's impact on the disease and the impact of the disease on the patient's attitudes. This diagnostic tool was designed to identify deficient areas in the functioning of the patient with chronic disease in order to undertake adequate therapeutic actions. The questionnaire consisted of 24 questions divided into three parts, with a catalogue of 5 answers added to each question. The high score for the entire questionnaire indicates the high physical and mental functioning of the surveyed persons. The high score related to the answers in consecutive subscales reflects patient's functioning respectively: the illness does not affect the patient's functioning; the patient believes she/he has a significant impact on the course of illness; the patient holds a very optimistic view for the future. The questionnaire is available free of charge on the website of the Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University in Poland (https://www.wnoz.cm.umk.pl/kizprzdr/narzedzia-badawcze-research-tools/) [5, 6].

The patients whose physical and mental status was not sufficient to independently consent to the study and fill in the questionnaires were excluded from the study. Of the 224 consecutive patients meeting the inclusion criteria, 22 of these did not fully complete at least one of the questionnaires. In total, 202 patients (129 men and 73 women) were included in the analysis. The mean (SD) age of the study group was 64.4 (11.6) years. The study cohort characteristics are presented in Table 1.

The statistical analysis was carried out using the Statistica 13.0 package (TIBCO Software Inc, California, USA). Continuous variables were presented as means with standard deviations. The Shapiro-Wilk test demonstrated the non-normal distribution of the investigated continuous variables. Therefore, non-parametric tests were used for statistical analysis. Comparisons between the two groups were performed with the Mann-Whitney unpaired rank-sum test. For comparisons between three or more groups, the Kruskal–Wallis one-way analysis of variance was used. Results were considered significant at $p < 0.05$. To identify factors with independent influence on FCIS score multiple regression analysis was performed. For finding the best model backwards stepwise regression was applied. Variables with a p-value of < 0.1 in univariate analysis were introduced into the multiple regression model. Subsequently, variables without significant impact ($p > 0.05$) were one after another removed from the multivariate model.

Results

The mean (SD) result of FCIS was 88.82 (± 10.98) points. Most respondents (44.55%) manifested a medium level of functioning in CAD [79 < result < 94 points]. Only 24.75% of patients achieved a low FCIS score [< 79 points]. The results of functioning in CAD (FCIS scores) in relation to selected sociodemographic and clinical factors are presented in Table 2.

Higher results in the subscale that describes the impact of the disease on the patient functioning were obtained by men, patients under 65 years old, working and with CAD duration less than a year. The earlier occurrence of myocardial infarction and previous PTCA and/or CABG were associated with strong beliefs about a significant impact of the disease on patients' functioning. The conviction about the possibility of influencing the course of the disease (subscale: patient's impact on the disease) was observed in men, patients remaining in a relationship and those who had a family member treated for CAD. On the other hand, patients after the CABG procedure held a weaker belief about the possibility of influencing the course of the disease. When assessing the impact of the disease on the patient's attitudes, it was noticed that optimism about the future was observed in patients remaining in a relationship and those with an average economic status.

In the univariate analysis, better functioning in the disease (FCIS overall score) was determined by male gender, remaining in a relationship, living in the countryside, average economic status and CAD duration of less than a year.

Multivariate analysis identified the economic status (average) was an independent factor contributing to better functioning in the disease. The CAD duration (1–5 years), marital status (widow/widower) and previous treatment with PTCA were independent factors contributing to the worse results in the FCIS scores. Regarding individual subscales, the independent factor determining the belief about the impact of the disease on the patient functioning was: the previous treatment with PTCA and/or CABG and age (> 65 years), while the belief about the possibility of influencing the course of the disease was independently influenced by gender (male) and the CAD duration (shorter than a year) (Tab. 3).

Table 1. Characteristics of the study group

Parameter	Variable	Total sample	
		N	%
Gender	Male	129	63.86
	Female	73	36.14
Age	< 65	89	44.06
	≥ 65	113	55.94
Place of residence	Country	52	25.74
	City	150	74.26
Education	Primary/vocational	109	53.96
	Secondary	70	34.65
	Higher	23	11.39
Self-reported economic status	Bad	28	13.86
	Satisfactory	163	80.69
	Good	11	5.45
Employment status	Pensioner/invalid	134	66.33
	Unemployed	11	5.45
	Employed	57	28.22
Marital status	Widowed	29	14.36
	Married/in a relationship	146	72.28
	Single	27	13.37
Family history of CVD	Yes	149	73.76
	No	53	26.24
Duration of CAD	< 1 year	72	35.64
	1–5 years	47	23.27
	> 5 years	83	41.09
Smoking status	Yes	55	27.23
	No	147	72.77
Body mass index	< 25 kg/m^2	52	25.74
	25–30 kg/m^2	83	41.09
	> 25 kg/m^2	67	33.17
Prior MI	Yes	75	37.13
	No	127	62.87
Prior PTCA	Yes	581	28.71
	No	144	71.29
Prior CABG	Yes	18	8.91
	No	184	91.09

Discussion

Faced with an illness, a person activates various mechanisms aimed at coping with the problem. Active behaviours focused on seeking information to control and influence one's illness seem to be the most beneficial. On the other hand, patient attitudes that are unfavourable to treatment, such as denial, fear or avoidance, may result from a subjective assessment of the situation inadequate to scientific knowledge [7, 8].

To the best of the authors' knowledge, the FCIS is a unique, validated tool that allows for a comprehensive

Table 2. The FCIS results depending on sociodemographic and clinical factors

Parameter/ /variable	N	The impact of illness on the patient	P	The patient's impact on the illness	P	The impact of illness on patents attitude	P	General result	P
Gender									
Male	129	28.22 ± 5.98	0.044	29.09 ± 4.29	0.002	31.22 ± 5.45	0.153	88.54 ± 11.07	0.003
Female	73	26.77 ± 5.19		27.10 ± 3.95		29.92 ± 6.42		83.78 ± 10.19	
Age									
< 65 years	89	28.83 ± 4.97	0.042	28.94 ± 3.77	0.080	30.28 ± 6.36	0.573	88.06 ± 11.07	0.086
≥ 65 years	113	26.81 ± 6.15		27.92 ± 4.59		31.12 ± 5.39		85.85 ± 10.85	
Marital status									
Widowed	29	26.21 ± 6.00	0.355	26.11 ± 4.45	0.009	28.59 ± 6.03	0.031	81.00 ± 11.92	0.014
Married/in a relationship	146	27.94 ± 5.81		28.82 ± 4.22		31.27 ± 5.68		82.02 ± 10.57	
Single	27	28.00 ± 4.91		28.30 ± 3.72		30.30 ± 6.11		86.59 ± 10.46	
Place of residence									
Country	52	28.56 ± 4.58	0.270	29.17 ± 4.19	0.121	31.38 ± 6.85	0.137	89.12 ± 10.98	0.049
City	150	27.40 ± 6.07		28.09 ± 4.28		30.53 ± 5.45		86.03 ± 10.90	
Education									
Primary/ vocational	109	27.34 ± 5.64	0.590	28.40 ± 4.21	0.630	30.98 ± 6.56	0.391	86.72 ± 11.26	0.841
Secondary	70	28.04 ± 6.28		28.17 ± 4.67		30.26 ± 5.01		86.47 ± 11.03	
Higher	23	28.35 ± 4.39		28.83 ± 3.34		31.17 ± 4.52		88.35 ± 9.69	
Employment status									
Pensioner/ ivalid	134	26.82 ± 6.00	0.019	28.22 ± 4.48	0.574	30.63 ± 5.86	0.660	85.67 ± 11.09	0.051
Unemployed	11	28.64 ± 4.11		28.09 ± 3.81		30.45 ± 4.08		87.18 ± 5.91	
Employed	57	29.58 ± 4.90		28.77 ± 3.87		31.11 ± 6.14		89.46 ± 11.14	
Self-reported economic status									
Bad	28	25.29 ± 6.64	0.072	27.71 ± 4.88	0.389	30.39 ± 7.06	0.021	83.39 ± 12.65	0.019
Satisfactory	163	28.15 ± 5.53		28.58 ± 4.21		31.13 ± 5.50		87.86 ± 10.47	
Good	11	27.18 ± 5.08		27.00 ± 3.41		26.00 ± 5.76		80.18 ± 10.66	
Family history of CVD									
Yes	149	27.88 ± 5.41	0.473	28.70 ± 4.25	0.040	30.78 ± 5.77	0.717	87.36 ± 11.52	0.183
No	53	27.19 ± 6.58		27.43 ± 4.24		30.68 ± 6.07		85.30 ± 9.22	
Duration of CAD									
< 1 year	72	28.99 ± 4.91	0.034	29.24 ± 3.87	0.082	31.26 ± 4.96	0.618	89.49 ± 10.37	0.016
1–5 years	47	26.32 ± 6.64		27.53 ± 3.88		30.02 ± 6.28		83.87 ± 10.97	
> 5 years	83	27.36 ± 5.69		28.10 ± 4.71		30.72 ± 6.29		86.18 ± 11.09	
Smoking status									
Yes	55	26.91 ± 5.00	0.083	29.15 ± 4.25	0.169	30.15 ± 5.74	0.301	86.20 ± 10.71	0.360
No	147	27.99 ± 5.98		28.08 ± 4.26		30.98 ± 5.88		87.05 ± 11.10	

→

Table 2 cont. The FCIS results depending on sociodemographic and clinical factors

Parameter/ /variable	N	The impact of illness on the patient	P	The patient's impact on the illness	P	The impact of illness on patents attitude	P	General result	P
Body mass index									
< 25 kg/m2	52	27.33 ± 5.42	0.439	27.67 ± 4.32	0.144	31.50 ± 4.87	0.681	86.50 ± 9.00	0.626
25–30 kg/m2	83	27.30 ± 5.80		28.72 ± 4.30		30.07 ± 6.70		86.10 ± 12.30	
> 30 kg/m2	67	28.48 ± 5.80		28.48 ± 4.20		31.01 ± 5.30		87.97 ± 10.80	
Prior MI									
Yes	75	26.59 ± 5.48	0.011	28.43 ± 4.82	0.847	30.97 ± 5.15	0.953	85.99 ± 10.64	0.259
No	127	28.35 ± 5.80		28.34 ± 3.93		30.62 ± 6.23		87.31 ± 11.18	
Prior PTCA									
Yes	58	25.79 ± 5.23	0.0006	28.71 ± 3.85	0.442	30.22 ± 6.88	0.808	84.72 ± 10.12	0.073
No	144	28.47 ± 5.77		28.24 ± 4.43		30.97 ± 6.88		87.67 ± 11.23	
Prior CABG									
Yes	18	23.33 ± 6.12	0.0009	26.22 ± 4.41	0.012	31.00 ± 4.95	0.933	80.56 ± 9.73	0.010
No	184	28.13 ± 5.53		28.58 ± 4.21		30.73 ± 5.93		87.43 ± 10.92	

Table 3. Independent factors determining FCIS result

Parameter	Direction component beta	Direction component beta standard error	P
FCIS I: The impact of illness on the patients			
Self-reported economic status - satisfactory	2.20	0.96	0.023
Age ≥ 65 years	-1.94	0.77	0.012
Prior PTCA	-2.17	0.85	0.012
Prior CABG	-3.72	1.36	0.007
FCIS II: The patient's impact on the illness			
Duration of CAD < 1 year	1.48	0.61	0.016
Gender – male	2.09	0.60	0.0007
FCIS III: The impact of illness on a patient's attitude			
No independent factors			
FCIS – General result			
Self-reported economic status – satisfactory	4.33	1.86	0.021
Marital status – widowed	-7.56	2.14	0.0005
Duration of CAD (1-5 years)	-4.68	1.75	0.008
Prior PTCA	-3.41	1.62	0.037

assessment of the functioning of patients with CAD. The current publication is the first scientific report, after the validation studies of the FCIS, to identify sociodemographic and clinical determinants of various aspects of functioning in chronic disease, in relation to CAD.

In previous studies of patients with cardiovascular diseases, better functioning in the physical and mental sphere was observed in men compared to women [9, 10]. Also, in the presented study men showed a higher FCIS score, mainly due to their belief that they could

influence and control the disease. The lower results obtained in women may be related to their tendency towards anxiety, chronic stress and depression [10]. Another study reported a better level of social functioning in women, while men reported a higher degree of vitality and mental health [11]. In the group of patients with atrial fibrillation, the female gender was an independent predictor of worse quality of life [12]. The study results suggest that men are characterized by better functioning in the disease, with the male gender being an independent factor that determines the belief that the patient can influence the course of the disease.

Higher results in the quality of life in terms of physical functioning were observed in younger people, while in terms of mental functioning - in the elderly [13, 14]. In this study, younger age was an independent factor determining the belief that the disease had a limited impact on the functioning of the patient.

We have observed that people who have lost a close person feel less able to influence their own illness. They also show lower mobilization to take an active attitude towards it, which is consistent with other reports regarding the quality of life [15, 16].

In one of the studies, the authors pointed out that living in the city is an independent factor in improving the quality of life in relation to the physical functioning of patients with atrial fibrillation [17]. In the presented study, better functioning in the CAD concerned people living in the countryside.

Lower socioeconomic status is associated with a higher prevalence of risk factors for cardiovascular diseases and a worse prognosis. When analyzing separate components of the socioeconomic status, the authors did not notice, similarly to Uchmanowicz et al. [15], any influence of education level on the functioning of patients with the disease. It was observed that work activity positively influences the functioning in CAD. This positive impact is manifested in the patient's conviction that the disease does not have a significant influence on one's life. Another study found that working people showed a high level of positive mental attitude and preventive behaviours assessed using the IZZ questionnaire [18]. In the authors' previous study it was showed that the attitude to employment positively influences the implementation of the therapeutic plan [19].

When assessing the economic status based on patients' declarations, it appeared that it is an independent factor influencing the FCIS result. Strong evidence for the association of socioeconomic status with the incidence of cardiovascular diseases and mortality is provided by the studies of Stringhini et al. [20], who indicated that it is an independent factor, comparable to traditional risk factors for cardiac events.

Earlier hospitalizations for cardiovascular events (myocardial infarction, PTCA and/or CABG procedure) and longer CAD duration were associated with worse functioning in the disease, especially in terms of the belief that the disease could affect the patient's functioning. The abnormal picture of the disease may be associated with insufficient medical knowledge on one's disease and low readiness for being discharged, which are closely related to the implementation of the therapeutic plan [21–26]. Therefore, it can be assumed that people who do not implement the therapeutic plan as a result of the conviction that it is impossible to influence the course of the disease are at an increased risk of health deterioration. Such an interpretation could justify lower FCIS scores in these patients.

Study limitations

The study did not take into account the patient's mental construct, which may affect the study outcomes.

Conclusions

1. The study allowed to identify independent factors that determine the functioning in the chronic disease, in relation to CAD.
2. The proposed tool comprehensively diagnoses patients' beliefs about the disease. Effective assessment of the quality of the patient's functioning in the disease may be useful in more individualized therapeutic management.

Conflict of interest: *The authors of the manuscript report no conflict of interest.*

References

1. Hawkes AL, Patrao TA, Ware R, et al. Predictors of physical and mental health-related quality of life outcomes among myocardial infarction patients. BMC Cardiovasc Disord. 2013; 13: 69, doi: 10.1186/1471-2261-13-69, indexed in Pubmed: 24020831.
2. Assari S, Lankarani MM, et al. Comorbidity influences multiple aspects of well-being of patients with ischemic heart disease. Int. Cardiovasc. Res. J. 2013; 7(118): 123.
3. Lalonde L, Clarke A, Joseph L, et al. Health-related quality of life with coronary heart disease prevention and treatment. Journal of Clinical Epidemiology. 2001; 54(10): 1011–1018, doi: 10.1016/s0895-4356(01)00361-4.
4. Olano-Lizarraga M, Oroviogoicoechea C, Errasti-Ibarrondo B, et al. The personal experience of living with chronic heart failure: a qualitative meta-synthesis of the literature. J Clin Nurs. 2016; 25(17-18): 2413–2429, doi: 10.1111/jocn.13285, indexed in Pubmed: 27273246.
5. Buszko K, Pietrzykowski Ł, Michalski P, et al. Validation of the Functioning in Chronic Illness Scale (FCIS). Medical Research Journal. 2018; 3(2): 63–69, doi: 10.5603/mrj.2018.0011.
6. Kubica A. Self-reported questionnaires for a comprehensive assessment of patients after acute coronary syndrome. Medical Research Journal. 2019; 4(2): 106–109, doi: 10.5603/mrj.a2019.0021.
7. Leksowska A, Jaworska I, et al. Somatic disease as an adaptation challenge for humans. Folia Cardiologica Excerpta. 2011; 6(4): 244–248.

8. Furmańska J, Pietrzak-Nowacka M, et al. Psychosocial determi-nants of the appraisal of disease significance by patients with a chronic disease. Człowiek i Społeczeństwo. 2018; XLV(245): 261.
9. Dueñas M, Ramirez C, Arana R, et al. Gender differences and determinants of health related quality of life in coronary patients: a follow-up study. BMC Cardiovasc Disord. 2011; 11: 24, doi: 10.1186/1471-2261-11-24, indexed in Pubmed: 21619566.
10. Dąbrowski R, Smolis-Bąk E, Kowalik I, et al. Quality of life and depression in patients with different patterns of atrial fibrillation. Kardiol Pol. 2010; 68(10): 1133–1139, indexed in Pubmed: 20967710.
11. Wojarska I. Emotional problems arising from chronic disease in patients staying in the cardiology department. Journal of Education, Health and Sport. 2017; 7(7): 226–23.
12. Jankowska-Polańska B, Kaczan A, Lomper K, et al. Symptoms, acceptance of illness and health-related quality of life in patients with atrial fibrillation. Eur J Cardiovasc Nurs. 2018; 17(3): 262–272, doi: 10.1177/1474515117733731, indexed in Pubmed: 28933196.
13. Veenstra M, Petterson KI, Rollag A, et al. Association of changes in health - related quality of life in coronary heard disease with coronary procedures and sociodemographic charakcteristics. Health Qual Life Outcomes 2004; 2. ; 56.
14. Pragodpol P, Ryan C. Critical review of factors predicting health-related quality of life in newly diagnosed coronary artery disease patients. J Cardiovasc Nurs. 2013; 28(3): 277–284, doi: 10.1097/JCN.0b013e31824af56e, indexed in Pubmed: 22495801.
15. Uchmanowicz I, Loboz-Grudzien K, Jankowska-Polanska B, et al. Influence of diabetes on health-related quality of life results in patients with acute coronary syndrome treated with coronary angioplasty. Acta Diabetol. 2013; 50(2): 217–225, doi: 10.1007/s00592-011-0280-2, indexed in Pubmed: 21442428.
16. Pałczak E, Uchmanowicz I, et al. Analysis of factors affecting quality of life following myocardial infarction . Piel. Zdr. Publ. . 2012; 2(1): 29–37.
17. Jankowska-Polańska B, Kaczan A, Lomper K, et al. Symptoms, acceptance of illness and health-related quality of life in patients with atrial fibrillation. Eur J Cardiovasc Nurs. 2018; 17(3): 262–272, doi: 10.1177/1474515117733731, indexed in Pubmed: 28933196.
18. Ślusarska B, Nowicki G. Health behaviours in prophylaxis of cardiovascular diseases among occupationally active population. Probl Hig Epidemiol. 2010; 91(1): 34–40.
19. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. Patient Prefer Adherence. 2018; 12: 333–340, doi: 10.2147/PPA.S150435, indexed in Pubmed: 29551891.
20. Stringhini S, Carmeli C, Jokela M, et al. LIFEPATH consortium. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. Lancet. 2017; 389(10075): 1229–1237, doi: 10.1016/S0140-6736(16)32380-7, indexed in Pubmed: 28159391.
21. Michalski P, Kosobucka A, Pietrzykowski Ł, et al. Effectiveness of therapeutic education in patients with myocardial infarction. Medical Research Journal. 2018; 2(3): 89–96, doi: 10.5603/mrj.2017.0011.
22. Michalski P, Kasprzak M, Siedlaczek M, et al. The impact of knowledge and effectiveness of educational intervention on readiness for hospital discharge and adherence to therapeutic recommendations in patients with acute coronary syndrome. Medical Research Journal. 2020, doi: 10.5603/mrj.a2020.0023.
23. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0005, indexed in Pubmed: 32037501.
24. Kubica A, Obońska K, Kasprzak M, et al. Prediction of high risk of non-adherence to antiplatelet treatment. Kardiol Pol. 2016; 74(1): 61–67, doi: 10.5603/KP.a2015.0117, indexed in Pubmed: 26101025.
25. Kubica A, Gruchała M, Jaguszewski M, et al. Adherence to treatment — a pivotal issue in long-term treatment of patients with cardiovascular diseases. An expert standpoint. Medical Research Journal. 2018; 2(4): 123–127, doi: 10.5603/mrj.2017.0016.
26. Kubica A, Bączkowska A. Rationale for motivational interventions as pivotal element of multilevel educational and motivational project MEDMOTION. Folia Cardiologica 2019; 15. ; 1: 6–10.

VIA MEDICA

ORIGINAL ARTICLE

Wioletta Szywacz, Sylwia Mielcarska, Alicja Szczerba, Agata Macionga, Nikola Szweda-Gandor, Władysław Grzeszczak

Department and Clinic of Internal Medicine, Diabetology and Nephrology, Medical University of Silesia, Zabrze, Poland

Influence of visfatin's gene variations on late diabetic complications

Corresponding author:
Wioletta Szywacz, SPSK No 1,
3-go Maja 13-15 Str.,
41-800 Zabrze, Poland,
e-mail: wiolettaszywacz@gmail.com

Medical Research Journal 2021;
Volume 6, Number 1, 28–32
10.5603/MRJ.a2021.0004

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Visfatin (nicotinamide phosphoribosyltransferase) is an adipokine that performs many functions in the organism. It can be expressed in different tissues such as the brain, kidneys and visceral adipose tissue. Visfatin takes part in many molecular processes including apoptosis, inflammation, cell proliferation. It affects glucose metabolism and is involved in the pathogenesis of diabetes, insulin resistance, atherosclerosis and obesity. Moreover, studies suggest that visfatin also may be associated with the development of diabetic nephropathy and retinopathy.

The goal of the study is the assessment of the influence of different visfatin's gene variants on the occurrence of late diabetic complications.

The study group consisted of 272 patients with diabetes – 139 men and 133 women from Southern Poland. Selected DNA fragments were amplificated and marked. Visfatin's gene in rs4730153 was examined. The Real-Time PCR was conducted with fluorescence-labelled probes.

The most common genotypes were heterozygote AG- 138 patients (51%) and homozygote GG- 89 patients (33%).

In the study group, there were 92 diabetics with retinopathy, 26 with nephropathy, 88 with neuropathy and 103 with macroangiopathy.

It has been assessed using the $\chi 2$ test that there are no differences between the variability of different variants of visfatin's gene in the distribution of genotypes. According to Hardy-Weinberg's test, the variety of population is maintained.

Key words: visfatin, diabetes mellitus, SNP, polymorphism, gene, late complications

Med Res J 2021; 6 (1): 28–32

Introduction

Diabetes mellitus is a silent pandemic of the 21st century [1]. Its prevalence is estimated to rise from 425 million people in 2017 to 629 million by 2045 [2]. Many patients with type 2 diabetes (T2DM) develop microvascular complications (approximately 40% of those develop diabetic kidney disease (DKD), which is a leading cause of the end-stage renal disease (ESRD) globally [3] and approximately 40–80% develop diabetic retinopathy (DR) [4]

DKD as well as DR are often diagnosed at advanced stages [5]. The multifactorial pathogenesis of DKD and DR consists of a combination of metabolic, environmental, and genetic factors [1]. A prior genome-wide association study (GWAS) identified genes with polymorphisms associated with an increased incidence of DKD and DR [6]. However, further studies to prove the role of these polymorphisms in DKD and DR occurrence and progression in different diabetic populations are needed, to guide strategies that prevent and treat DKD and DR.

Visfatin, a recently discovered adipocytokine is the extracellular isoform of the NAMPT enzyme. Its gene is located on chromosome 7 and the exact location is as follows: band 7q22.3, starting 106,248,298 bp, ending 106,286,326 bp. Visfatin can cause an insulin-mimetic effect in cells. As it downregulates the amount of glucose release from the liver, visfatin accelerates triglycerides synthesis and increases glucose metabolism in monocytes and adipocytes. It plays an important role in the pathogenesis of T2DM and its complications such as diabetic nephropathy and retinopathy. Nevertheless, there are limited studies about the association between visfatin and diabetic complications in these diseases.

The role of visfatin in diabetic retinopathy is poorly understood. In humans, only one study investigated the

differences in visfatin concentrations between patients with and without diabetic retinopathy. Y. Wang et al. have found elevated vitreous and serum level of visfatin in diabetic patients with proliferative diabetic retinopathy compared to these with nonproliferative diabetic retinopathy, without diabetic retinopathy and nondiabetic controls [7].

Patients with diabetic nephropathy show markedly increased serum levels of visfatin comparing to the non-diabetic group [8–10]. Mageswari R et al. suggest that visfatin level could be an index of severity of diabetic kidney disease. Many studies are investigating the role of Single Nucleotide Polymorphism (SNP) in the visfatin gene. It has been researched that the variations are involved in the pathogenesis of diabetes, obesity as well as may regulate plasma insulin levels and plasma glucose levels.

In light of the positive GWAS outcomes in relation to the visfatin gene and the contradictory outcomes of follow-up studies — as well as the lack of studies performed in a Polish population — this study assessed the association of rs4730153 visfatin gene variants with DKD and DR in a group of Polish T2DM patients (the industrial region of Silesia, Poland).

The presented study is the first one to investigate the influence of SNP in the visfatin gene on diabetic retinopathy and nephropathy occurrence.

Materials and methods

Materials used for this genetic study were samples of venous blood taken from willing subjects. All patients partaking in this study have signed written consent. The study group consisted of 272 individuals. Among them, 139 were men and 133 women. All of these patients had been previously diagnosed with T2DM.

For the time needed to gather the representative group for research, blood samples collected from subjects were stored at the proper temperature at minus 70 Celsius degrees.

In the laboratory of Clinical Hospital 1 in Zabrze, the DNA material was isolated from obtained blood. The next step was to prepare a proper concentration of the DNA which was 15 ng/μl. Then with a spectrophotometer, the purity of samples was checked.

Using fluorescent-labelled TaqMan Pre-designed SNP Genotyping Assay probes allelic discrimination was performed in Roche Lightcycler 96 thermocycler. Alleles were marked as A in VIC and G in FAM.

Finally, statistical analysis was made to present the result of the study. The significance between distributions of genotypes and alleles, presence of diabetic retinopathy, nephropathy, neuropathy and macroangiopathy were tested using Pearson's $\chi 2$ test. Non-parametric ANOVA analysis was used to examine the association of visfatin polymorphism in rs4730153 with the occurrence of late complications of diabetes mellitus. P values < 0.05 were considered statistically significant. The statistical software STATISTICA 13 for Windows (TIBCO Software Inc., Palo Alto, CA, USA) was used to perform all analyses.

Results

In order to analyze the dependence between visfatin's gene in rs4720153 and late complications of T2DM, the number of each patients' alleles and genotypes were profiled with clinical data and occurrence of complications.

Among studied patients 29 were in the healthy weight range (10,5%), 115 overweight (42,5%) and 128 obese (47%) due to the WHO Body Mass Index (BMI) (Tab.1). The waist to hip ratio (WHR) of patients was also assessed with similar results: 17 patients with normal ratio (6,25%), 64 over-weight (23,5%) and 191 obese (70,25%).

Genotype distribution of the patients complied with populational- presented heterozygote (AG) genotype occurred most often (51%) with AA or GG respectively 17 and 33%. The distribution was compatible with Hardy-Weinberg equilibrium (Tab. 2).

Regarding treatment schedule, at the moment of testing 101 individuals were treated with insulin injections, 171 were taking oral medicaments and 72 were prescribed both of them. Hypertension was present in 74.3% of patients (202 patients). Patients with dyslipidaemia stated 54,8 % (149) of all group.

Table 1. Distribution of genotypes of visfatin's SNP in rs4730153 in reference to BMI

		Normal body weight	Overweight	Obese
AA	n	4	26	15
	%	9	58	33
AG	n	15	57	66
	%	11	41	48
GG	n	10	32	47
	%	11	36	53

p = 0,1962

Table 2. Distribution of genotypes of visfatin's SNP in rs4730153 in the research group

Genotype	Amount of carriers	Percentage of group
AA	45	17%
AG	138	51%
GG	89	33%

Table 3. Distribution of genotypes of visfatin's SNP in rs4730153 in reference to retinopathy occurrence

Genotypes	With retinopathy		Without retinopathy		p-value	OR (95% CI)
	N	%	N	%		
AA	13	28.89	32	71.11	-	1.00 (Reference)
AG	43	31.16	95	68.84	0.7742	1.114 (0.532–2.332)
GG	36	40.45	53	59.55	0.1914	1.672 (0.773–3.615)
AG+GG	79	34.80	148	65.20	0.4447	0.761 (0.378–1.533)

Table 4. Distribution of genotypes of visfatin's SNP in rs4730153 in reference to nephropathy occurrence

Genotypes	With nephropathy		Without nephropathy		p-value	OR (95% CI)
	N	%	N	%		
AA	2	4.44	45	95.56	-	1.00 (Reference)
AG	12	8.70	126	91.30	0.3606	2.048 (0.441–9.518)
GG	12	13.48	77	86.52	0.1245	3.351 (0.716–15.673)
AG+GG	24	10.57	203	89.43	0.2165	2.542 (0.579–11.162)

Table 5. Distribution of genotypes of visfatin's SNP in rs4730153 in reference to neuropathy occurrence

Genotypes	With neuropathy		Without neuropathy		p-value	OR (95% CI)
	N	%	N	%		
AA	16	35.56	29	64.44	-	1.00 (Reference)
AG	37	26.81	101	73.19	0.2631	0.664 (0.324–1.360)
GG	35	39.33	54	60.67	0.6713	1.175 (0.558–2.472)
AG+GG	72	31.72	155	68.28	0.6155	0.842 (0.430–1.648)

Four late complications of T2DM in anamnesis were taken into consideration: retinopathy, nephropathy, peripheral neuropathy and macroangiopathy. The conducted analysis provided results as presented below.

Retinopathy occurred in 92 patients (33,8%). Regarding all of the patients, there were more without the retinopathy among AA and AG genotype. The above indicates more people with genotype GG developing this T2DM complication (Tab. 3).

Nephropathy was present in 26 cases (9,6%). Out of the patients who did not suffer from nephropathy 51% stated AG genotype. The greatest difference can be seen in the GG genotype: 46 % among a group of occurred by retinopathy to only 31% among patients without this complication (Tab. 4).

Considering the next studied complication, 88 patients of the T2DM group had neuropathy, which is 32,3% of all. With a slight difference of occurrence in AA genotype, the other two presents as follows: more non-neuropathy patients in comparison to ones with neuropathy in AG genotype and consequently, less patient without this complication than those with neuropathy in GG genotype (Tab. 5).

Macroangiopathy showed most often occurrence. 37,9 % of the studied patients (103) had already been diagnosed with the disease while genotype determining. In this case, the group with AA and GG genotype have not significantly more patients with the complication (Tab. 6).

24 (8,8%) of patients suffered from macroangiopathy and neuropathy altogether. Most of them presented GG genotype (45,8%), second AG (37,5%) and 16,7% AA genotype.

Only 6 (2,2%) individuals presented all of the mentioned complications.

We may note among all of the studied complications is that in the AG genotype group there are always more patients without the disease than with one. Exactly opposite we may note in GG genotype in all of the studied cases.

No statistically significant differences in genotype distribution between groups in all researched areas have been observed.

Table 6. Distribution of genotypes of visfatin's SNP in rs4730153 in reference to macroangiopathy occurrence

Genotypes	With macroangiopathy		Without macroangiopathy		p-value	OR (95% CI)
	N	%	N	%		
AA	19	42.22	26	57.78	-	1.00 (Reference)
AG	49	35.51	89	64.49	0.4190	0.753 (0.379–1.497)
GG	35	39.33	54	60.67	0.7469	0.887 (0.428–1.838)
AG+GG	84	37.00	143	63.00	0.5103	0.804 (0.420–1.540)

Discussion

The study aimed to investigate the correlation between different variants of the visfatin gene in rs 4730153 and the occurrence of late complications of T2DM in the population of Southern Poland. The authors wanted to assess whether the studied SNP of the visfatin gene is associated with an increased risk of developing late complications of diabetes.

T2DM is a growing problem nowadays; in 2013 there were 3 million patients diagnosed with diabetes in Poland [11]. What is more, 30% of patients diagnosed with myocardial infarction have also diabetes; one in seven patients with newly diagnosed diabetes will develop acute coronary syndrome in the next 10 years, 60% of patients with a duration of diabetes of more than 15 years have retinopathy and 15% – nephropathy [12].

As has been mentioned, the level of proinflammatory visfatin is elevated in patients with diabetes mellitus. Many studies indicate that visfatin may lead to vascular disorders in different mechanisms: visfatin ability to induce MMP-9 and nuclear factor-κB which are involved in the instability of atherosclerotic plaque.

Moreover, visfatin may be engaged in endothelial dysfunction [13]. It has been shown that in diabetic macroangiopathy the level of serum visfatin is significantly lower in comparison to patients with non-complicated diabetes. Additionally, the serum level of visfatin can be negatively correlated with the lipid profile [14].

It was described that visfatin as an adipokine with proangiogenic features may take some role in the pathogenesis of diabetic retinopathy. In patients with diabetic retinopathy, the concentration of visfatin in serum and vitreous is elevated and correlated with the severity of the disease [15].

It has been reported that visfatin may stimulate the expression of endothelial nitric oxide in renal cells in patients with diabetic nephropathy. This observation seems to be confirmed by the fact that patients with diabetic nephropathy have an increased level of visfatin in serum [16] especially in the IV stage of disease in comparison to stage III [17]. The level of visfatin in serum can predict the severity of diabetic nephropathy.

There are only several pieces of research that investigated the role of visfatin polymorphism in rs4730153. One of them indicates that there is no association between T2DM and studied SNP, however, the ratio visceral/subcutaneous visfatin expression is correlated with visfatin polymorphism in rs4730153 [18].

Other studies note the role of rs4730153 in the pathogenesis of obesity; it was also described that plasma visfatin level is increased in patients with obesity. One study indicates that genotype AA in rs4730153 of visfatin gene may decrease the risk of cardiovascular disorders both in patients with normal body weight and with obesity. Variant AA of the rs4730153 is related to fasting blood glucose, fasting blood insulin and HOMA-IR (homeostasis model assessment-insulin resistance) [19].

Other research was carried out on Chinese obese children taking part in the aerobic exercise training program. It has observed statistically significant differences in the level of triacylglycerols (TG) and HOMA-βvalue before and after the exercise programme according to genotype in rs4730153. Genotype GG seems to reduce TG level and increase sensitivity to insulin-induced by exercises [20].

There are contradictory data on the association between rs4730153 and BMI; some studies suggest that there is no association between rs4730153 and BMI [18], but on the other hand another one shows a borderline significant correlation between rs4730153 and decreased BMI [21].

The presented study was carried out since there are no other available studies about the role of visfatin polymorphism in rs4730153 in long term complications of diabetes mellitus. This study is the first one that investigated the association between visfatin polymorphism and late complications of diabetes. The authors had not observed any statistically significant association between different variants of the visfatin gene in rs 4720153 and the occurrence of late complications of diabetes. However, the duration of diseases and intensity of glycemic control influence strongly the development of diabetes complications [22]. Also, the disproportion in the number of patients

with/without specific complications could have affected the results.

This study had some limitations: the concentration of visfatin in serum was not measured; the expression of visfatin by measuring visfatin mRNA was also not examined, so it could not have been assessed how studied SNP influences visfatin expression. Further studies with a complete assessment of visfatin expression not only in serum but also in organs involved in diabetic complications are necessary to assess the role of visfatin polymorphism in rs4730153 in the development of long term complications of diabetes mellitus.

In comparison to other visfatin's SNPs, rs4720153 is yet to be widely researched.

Conclusions

Collected data showed that SNP in rs4730153 of visfatin using $\chi 2$ test does not show a statistically significant correlation in any of the late complications of T2DM. All of the complications were present more often in heterozygote patients (AG) which may result from the largest group of patient with the genotype. Most tested patients were obese and suffered already from hypertension and dyslipidaemia.

Because of a quite small group and not much of any other research on this polymorphism, further study is needed to know the role of SNP of visfatin in T2DM late complications.

Acknowledgements: *The authors would like to thank Władysław Grzeszczak and the Department of Internal Medicine, Diabetology and Nephrology in Zabrze for the idea and for helping financially with the research. The authors wish to show their appreciation to Nikola Szweda who supported them in every part of the research. The authors thank for support in laboratory: Wanda Trautsolt and Sylwia Górczyńska-Kosiorz.*

List of abbreviations:

T2DM — Type 2 Diabetes Mellitus
WHO — World Health Organization
SNP — single nucleotide polymorphism
BMI — Body Mass Index
WHR — Waist to hip ratio
TG — triacylglycerols
HOMA-IR — homeostasis model assessment-insulin resistance

Statement of competing interests: *The authors report no competing interests.*

References

1. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World J Diabetes. 2015; 6(6): 850–867, doi: 10.4239/wjd.v6.i6.850, indexed in Pubmed: 26131326.
2. International Diabetes Federation. IDF Diabetes Atlas, 8th ed. : Brussels.
3. American Diabetes Association. 11. Microvascular Complications and Foot Care: . Diabetes Care. 2019; 42(Suppl 1): S124–S138, doi: 10.2337/dc19-S011, indexed in Pubmed: 30559237.
4. Sorrentino FS, Matteini S, Bonifazzi C, et al. Diabetic retinopathy and endothelin system: microangiopathy versus endothelial dysfunction. Eye (Lond). 2018; 32(7): 1157–1163, doi: 10.1038/s41433-018-0032-4, indexed in Pubmed: 29520046.
5. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. Kidney Int Suppl (2011). 2018; 8(1): 2–7, doi: 10.1016/j.kisu.2017.10.003, indexed in Pubmed: 30675433.
6. Ahlqvist E, van Zuydam NR, Groop LC, et al. The genetics of diabetic complications. Nat Rev Nephrol. 2015; 11(5): 277–287, doi: 10.1038/nrneph.2015.37, indexed in Pubmed: 25825086.
7. Wang Y, Yuan Ye, Jiang H. Serum and vitreous levels of visfatin in patients with diabetic retinopathy. Med Sci Monit. 2014; 20: 2729–2732, doi: 10.12659/MSM.891292, indexed in Pubmed: 25524991.
8. Mahmood N, Junejo AM, Jamal Q, et al. Association of visfatin with chronic kidney disease in a cohort of patients with and without diabetes. J Pak Med Assoc. 2010; 60(11): 922–6.
9. Kang YS, Cha DR. The role of visfatin in diabetic nephropathy. Chonnam Med J. 2011; 47(3): 139–143.
10. Mageswari R, Sridhar MG, Nandeesha H, et al. Irisin and Visfatin Predicts Severity of Diabetic Nephropathy. Indian J Clin Biochem. 2019; 34(3): 342–346, doi: 10.1007/s12291-018-0749-7, indexed in Pubmed: 31391726.
11. Cukrzyca. Ukryta pandemia. Sytuacja w Polsce. : Edycja.
12. Kalbarczyk WP, Okopień B. Cukrzyca: gdzie jesteśmy? dokąd zmierzamy?: Raport Instytutu Ochrony Zdrowia. Warszawa: Instytut Ochrony Zdrowia. ; 2018.
13. Liang W, Ye DD. The potential of adipokines as biomarkers and therapeutic agents for vascular complications in type 2 diabetes mellitus. Cytokine Growth Factor Rev. 2019; 48: 32–39, doi: 10.1016/j.cytogfr.2019.06.002, indexed in Pubmed: 31229411.
14. Alghasham AA, Barakat YA. Serum visfatin and its relation to insulin resistance and inflammation in type 2 diabetic patients with and without macroangiopathy. Saudi Med J. 2008; 29(2): 185–192, indexed in Pubmed: 18246224.
15. Wang Y, Yuan Ye, Jiang H. Serum and vitreous levels of visfatin in patients with diabetic retinopathy. Med Sci Monit. 2014; 20: 2729–2732, doi: 10.12659/MSM.891292, indexed in Pubmed: 25524991.
16. Akbarian N, Zarghami N, Mota A, et al. Correlation Between Circulating Visfatin and Nitric Oxide Metabolites Levels in Patients With Diabetic Nephropathy. Iran J Kidney Dis. 2018; 12(3): 163–168, indexed in Pubmed: 29891746.
17. Mageswari R, Sridhar MG, Nandeesha H, et al. Irisin and Visfatin Predicts Severity of Diabetic Nephropathy. Indian J Clin Biochem. 2019; 34(3): 342–346, doi: 10.1007/s12291-018-0749-7, indexed in Pubmed: 31391726.
18. Böttcher Y, Teupser D, Enigk B, et al. Genetic variation in the visfatin gene (PBEF1) and its relation to glucose metabolism and fat-depot-specific messenger ribonucleic acid expression in humans. J Clin Endocrinol Metab. 2006; 91(7): 2725–2731, doi: 10.1210/jc.2006-0149, indexed in Pubmed: 16636125.
19. Martínez Larrad MT, Corbatón Anchuelo A, Fernández Pérez C, et al. Segovia Insulin Resistance Study Group (SIRSG). Obesity and Cardiovascular Risk: Variations in Visfatin Gene Can Modify the Obesity Associated Cardiovascular Risk. Results from the Segovia Population Based-Study. Spain. PLoS One. 2016; 11(5): e0153976, doi: 10.1371/journal.pone.0153976, indexed in Pubmed: 27166797.
20. Lai A, Chen W, Helm K. Effects of visfatin gene polymorphism RS4730153 on exercise-induced weight loss of obese children and adolescents of Han Chinese. Int J Biol Sci. 2013; 9(1): 16–21, doi: 10.7150/ijbs.4918, indexed in Pubmed: 23289013.
21. Rong J, Chu M, Xing B, et al. Variations in the gene are associated with body mass index: A population-based study in northern China. Meta Gene. 2015; 6: 65–68, doi: 10.1016/j.mgene.2015.08.004, indexed in Pubmed: 30941280.
22. Melmer A, Laimer M. Treatment Goals in Diabetes. Endocr Dev. 2016; 31: 1–27, doi: 10.1159/000439364, indexed in Pubmed: 26824869.

VIA MEDICA

ORIGINAL ARTICLE

Serkan Elarslan, Özlem Güdük, Yaşar Sertbaş

University of Sciences, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

Clinical characteristics of health care workers infected with COVID-19 at the Single-Center Hospital in Turkey

Corresponding author:

Özlem Güdük, University of Sciences, Fatih Sultan Mehmet Training and Research Hospital, 34752 Istanbul, Turkey, e-mail: gudukozlem@gmail.com

Medical Research Journal 2021; Volume 6, Number 1, 33–39
10.5603/MRJ.a2021.0005

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: COVID-19 is a highly infectious disease characterized by different symptoms and varying severity from person to person. This study aims to identify the clinical characteristics of healthcare workers (HCWs) who have been infected with coronavirus and investigate which factors affect the disease's severity.

Materials and methods: In the presented study, 79 healthcare workers (HCWs) were recruited who had been infected with SARS-CoV-2, and working in a training and research hospital. Their data was examined in two groups as uncomplicated (without a computed tomography sign of pneumonia and respiratory rate < 24 per minute, SpO2 $> 93\%$ at room air) and pneumonia group in terms of the severity of the disease. The statistical analysis was performed by SPSS v.22.0 with a statistical significance of 0.05.

Results: A total of 79 HCWs with a mean age of 33.37 ± 8.44 years were enrolled in the study. They consisted of 47 female and 32 male participants. There were 50 patients in uncomplicated and 29 patients in the pneumonia group. A total of 14 HCWs have been hospitalized with an average stay of 5.43 ± 1,5 days. The number of hospitalization between the groups was higher in the pneumonia group (n: 11) than in the uncomplicated group (n: 3) (38% *vs.* 6%; $p < 0.001$). HCWs who work in areas in close contact with the patient (high-risk units) were more prone to be in the pneumonia group than those working in the other areas of the hospital [22/45 (48%) *vs.* 7/27 (25%); $p = 0.019$]. There wasn't any significant difference between the groups in terms of age, gender, occupation, and the presence of chronic illness of workers ($p > 0.05$). Sore throat and cough were the most common onset symptoms of the disease (34.2% and 31.6%, respectively). There was no difference between the groups in terms of biochemical parameters. ($p > 0.05$).

Conclusion: Healthcare workers are in the risk group for COVID-19 disease. HCWs working in high-risk units are more vulnerable.

Key words: COVID-19 outbreak, coronavirus, healthcare workers, disease's severity

Med Res J 2021; 6 (1): 33–39

Introduction

The novel Coronavirus disease (COVID-19) is a highly infectious disease leading to significant morbidity and mortality. The disease first appeared in Wuhan and spread rapidly throughout the world, causing havoc in the 21st century [1, 2]. The first patient in Turkey was diagnosed on March 11, 2020. A total of 2.355.839 people got caught with the disease, and 23.325 people have died from that time to January 13, 2020, in the country [3]. In addition to affecting the entire society, the disease has also caused a significant number of deaths among healthcare workers (HCWs). According to the International Council of Nurses, it is estimated that 1,500 nurses in 44 countries died from COVID 19, and HCWs deaths from COVID 19 could amount to more than 20,000 worldwide [4].

Due to the high contagiousness of the disease, early diagnosis, isolation, and treatment are essential. Primary diagnostic uses include; computed tomography (CT) imaging and real-time reverse-transcriptase-polymerase chain reaction (RRT-PCR) [5]. In general, the radiographic features of the coronavirus are similar to those found in community-acquired pneumonia caused by other organisms. However, in terms of the CT image, COVID-19 pneumonia can be differentiated from non-COVID-19 pneumonia [6]. While COVID-19 pneumonia is more likely to have

a peripheral distribution, ground-glass opacity, fine reticular opacity, and vascular thickening, it has less likely to have a central+peripheral distribution, pleural effusion, and lymphadenopathy [7].

Infection of the virus causes various effects on individuals. Although most people recover without requiring special treatment, the elderly and people with medical problems are more likely to develop illnesses seriously [8]. The most common clinical symptoms of the disease are fever, cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhea [9], and radiological findings compatible with bilateral lung pneumonic infiltration. Besides, diarrhoea and vomiting are rare symptoms. Some patients may experience some degree of dyspnoea as an onset symptom. However, respiratory symptoms usually develop from several days to a week after the onset of the illness. Although the disease can be asymptomatic, pneumonia and severe acute respiratory tract infection may occur in 20–30% of the cases. Furthermore, renal failure and even death may develop in severe cases [10–12].

HCWs are inevitably at risk against COVID-19 disease. According to the Report of Amnesty International, at least 7,000 healthcare workers have died around the world after contacting COVID-19 until the beginning of September 2020 [13, 14]. Yet, little is known about the health status, basic demographics, severity of the disease, and computed tomography images of the healthcare workers receiving treatment for the disease. That's why more studies investigating the effects of COVID-19 disease on healthcare professionals are needed. This study aims to identify the clinical characteristics of HCWs who were infected with coronavirus and to investigate which factors affect the disease's severity.

Materials and methods

Sample

This is a single-centred, retrospective study of a group of HCWs infected with COVID-19 working at a training and research hospital. The demographic and clinical characteristics of data of the HCWs who had applied to the Occupational Health & Safety Unit of the hospital with the diagnosis of coronavirus were collected from the hospital information system (HIS). The fact that the first employee applied on March 26, 2020, was the starting date for collecting data. In the study, the authors included all the admissions of HCWs to the hospital for seven months from the onset of the disease. The data about the age, sex, occupation, chronic diseases (e.g., hypertension, diabetes, etc.) of the workers were collected, as were their departments, symptoms, and laboratory test results (e.g., albumin, bilirubin, C-reactive protein, D-dimer, etc.) at the onset, radiologic assessments of chest CT, and hospitalization status.

We classified healthcare workers in terms of their clinical condition. For this purpose, the authors used "the COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment Guideline" set by Scientific Advisory Board working under the Turkish Health Ministry. According to the guideline, people are categorized into three groups. These are uncomplicated patients, patients with pneumonia, and patients in need of intensive care [15].

— Uncomplicated patients:
  - Fever, muscle/joint pain, cough, and sore throat without respiratory distress (respiratory rate < 24 per minute, SpO2 > 93% at room air),
  - Patients with normal chest x-ray and/or lung tomography.
— Patients with pneumonia:
  - Fever, muscle/pains, cough and sore throat, respiratory rate < 30 per minute, SpO2 level > 90% in room air,
  - Patients with signs of mild to moderate pneumonia on chest radiography or tomography.
— Patients in need of intensive care:
  - Dyspnoea and respiratory distress,
  - Respiratory rate ≥ 30 per minute,
  - PaO2/FiO2 < 300,
  - Oxygen need increase in follow-up
  - SpO2 < 90% or PaO2 < 70 mmHg despite 5 L/min oxygen therapy,
  - Hypotension (systolic blood pressure < 90 mmHg and a decrease from usual SBP more than 40 mmHg and mean arterial pressure < 65 mmHg, tachycardia > 100/min,
  - Acute kidney damage, acute liver function test disorder,
  - Patients with the development of acute organ dysfunction such as confusion, acute bleeding diathesis, and immunosuppression,
  - High Troponin level and arrhythmia,
  - Lactate > 2 mmol,
  - Patients who meet the criteria for the presence of skin disorders such as capillary return disorder are evaluated to be treated in the intensive care unit.

In this study, the category of "patients in need of intensive care" was not udes since none of the workers needed intensive care treatment. Thus, healthcare workers were divided into two groups; (a) patients with typical CT signs and only positive PCR tests under the "uncomplicated" category (b) patients with CT results consistent with signs of pneumonia under the "pneumonia" category.

Table 1. Demographic data of the patients

Variable		Total	Uncomplicated	Pneumonia	p-value
Age: mean ± SD (range)		34.37 ± 8.4 (20–57)	32.26 ± 7.22 (20–52)	36.28 ± 9.39 (22–57)	0.189
Hospitalization: patients (%)		14 (18%)	3 (6%)	11 (38%)	0.000
Gender	Female	47 (59.5)	33 (66)	14 (48.3)	0.191
	Male	32 (40.5)	17 (34)	15 (51.7)	
Occupation	Doctor	18 (22.8)	12 (24)	6 (20.7)	0.944
	Nurse	29 (36.7)	18 (36)	11 (37.9)	
	Others	32 (40.5)	20 (40)	12 (41.4)	
Units	High risk	45 (57)	23 (46)	22 (75.9)	0.019
	Low risk	34 (43.0)	27 (54)	7 (24.1)	

Units, where HCWs work, were evaluated under two groups as "high-risk units" and "low-risk units" in terms of the contact possibility with COVID-19 patients. High-risk units consisted of the emergency department, the operating room, the anaesthesia clinic, and the clinics where COVID-19 patients were diagnosed and treated. Those other than these units were defined under the "low-risk units" category.

Statistical analysis

The data were evaluated with SPSS v.22.0 program. Mann Whitney U test was used for two independent groups analysis, and Chi-Square tests (Yates', Fisher's Exact, Pearson Chi-Square) were used for categorical variables. Statistical significance was accepted at $p < 0.05$ level.

The study was approved by the hospital Ethics Committee with the number 2020/28 and the date of 11/06/2020.

Results

Between the periods of March 26, 2020, to November 02, 2020, a total of 79 HCWs had been registered with COVID-19 diagnosis by the hospital's occupational health unit. These patients' sex distribution was as follows; 47 female (59.5%), 32 male (40.5%), were registered. The mean age of the total HCWs was 33 ± 8.44 years. Of the total participants, 50 (63.3%) were in the uncomplicated group, and 29 (36.7%) were in the pneumonia group.

A total of 14 HCWs have been hospitalized with an average stay of 5.43 ± 1,5 days. Patients in the pneumonia group were more prone to be hospitalized as seen in Table 1 (38% *vs.* 6%; $p < 0.001$) All the inpatient cases investigated in this study discharged and none died.

There was no difference between the distribution of participants in terms of working as doctor, nurse or in other situations ($p = 0.944$). In terms of the working units, most of the participants in the pneumonia group were working in high-risk units of the hospital. 22/29 (75.9%) *vs.* 7/29 (24.1%); $p = 0.019$. Most of the employees in the pneumonia group consisted of workers working in the high-risk units. There weren't significant differences among the age and sex distribution of participants between uncomplicated and complicated groups.

In Table 2 were compared the chronic disease histories and symptoms during COVID-19 disease, depending on whether the participants were in the complicated or uncomplicated group.

When the workers' presences of chronic diseases were analysed, it was found that 16 healthcare workers diagnosed with nine different chronic diseases. Three of these workers had more than one disease. The most common chronic diseases among workers were hypertension, asthma, and diabetes mellitus. No significant relationship was found between the prognosis of COVID-19 and any of those nine chronic diseases ($p > 0.05$).

Sore throat, cough, malaise/weakness/fatigue, shortness of breath, and fever were the most common onset symptoms of HCWs. On the other hand, only one worker experienced stinging during breathing, and one worker had dysuria. None of the signs & symptoms had a significantly important difference between the groups ($p > 0.05$).

There was no significant difference between the groups in terms of their biochemical blood parameters ($p > 0.05$) (Tab. 3).

Table 2. Chronic illness history of participants and symptoms of participants during the period of having COVID-19 infection

Variable		Total n (%)	Uncomplicated n (%)	Pneumonia n (%)	p value
		79 (100)	**50 (63.3)**	**29 (36.7)**	
Chronic illness	Hypertension	6 (7.6)	2 (4)	4 (13.8)	0.185
	Asthma	5 (6.3)	3 (6)	2 (6.9)	0.610
	Diabetes mellitus	4 (5.1)	2 (4)	2 (6.9)	0.622
	Hypothyroidism	2 (2.5)	0	2 (6.9)	
	Peripheral venous insufficiency	2 (2.5)	2 (4)	0	
	Fibromyalgia	1 (1.3)	1 (2)	0	
	Chronic allergy	1 (1.3)	1 (2)	0	
	COPD	1 (1.3)	1 (2)	0	
	Hashimoto	1 (1.3)	0	1 (3.4)	
Comorbidity	Yes	3 (3.8)	1 (2)	2 (6.9)	
Signs & Symptoms	None	4 (5.1)	3 (6)	1 (3.4)	
	Sore throat	27 (34.2)	20 (40)	7 (24.1)	0.235
	Cough	25 (31.6)	14 (28)	11 (37.9)	0.507
	Malaise / weakness / fatigue	24 (30.4)	18 (36)	6 (20.7)	0.241
	Shortness of breath	13 (16.5)	6 (12)	7 (24.1)	0.211
	Fever	12 (15.2)	6 (12)	6 (20.7)	0.341
	Headache	7 (8.9)	5 (10)	2 (6.9)	1.000
	Diarrhea	6 (7.6)	3 (6)	3 (10.3)	0.367
	Common body pain	6 (7.6)	4 (8)	2 (6.9)	
	Feeling cold	5 (6.3)	3 (6)	2 (6.9)	
	Chills	5 (6.3)	3 (6)	2 (6.9)	
	Runny nose	5 (6.3)	4 (8)	1 (3.4)	
	Chest pain	4 (5.1)	1 (2)	3 (10.3)	
	Back pain	4 (5.1)	1 (2)	3 (10.3)	
	Abdominal pain	3 (3.8)	2 (4)	1 (3.4)	
	Joint pain	3 (3.8)	1 (2)	2 (6.9)	
	Loss of taste and smell	2 (2.5)	1 (2)	1 (3.4)	
	Sweating	2 (2.5)	1 (2)	1 (3.4)	
	Stinging during breathing	1 (1.3)	0	1 (3.4)	
	Dysuria	1 (1.3)	0	1 (3.4)	

COPD — chronic obstructive pulmonary disease

Discussion

In this study, the clinical characteristics of healthcare workers diagnosed with coronavirus over seven months in a training and research hospital were evaluated according to the severity of the disease. Employees were examined in two groups (uncomplicated, pneumonia). Of the total participants, 63.3% were in the uncomplicated group, 36.7% in the pneumonia group. According to personal data (age, gender, job, unit of work, presence of chronic disease), the differences between the two groups and the initial symptoms and blood test results related to COVID-19 were examined.

It was found that the number of female workers was higher among diagnosed workers. Various studies find the different rates of female and male healthcare workers getting infected with COVID-19. In some studies, similar to ours, the rate of females was higher than males [16, 17]. It is thought that the higher number of female employees in hospitals, in general, may affect

Table 3. Comparison of the blood parameters of the groups

	Parameters	Uncomplicated n (%)	Pneumonia n (%)	Z	P-value
		Median	Median		
Blood tests	Albumin [g/L]	44.5	45.2	-0.753	0.474
	Bilirubin [direct][mg/dL]	0.20	0.29	-1.121	0.218
	C-reactive protein [mg/dL]	0.40	0.71	-1.426	0.156
	D-dimer [ng/mL]	0.40	75.18	-0.943	0.346
	White blood cells [10^3/uL]	6.30	7.10	-0.605	0.545
	Red blood cells [10^6/uL]	4.95	5.04	-0.063	0.950
	Hemoglobin [g/dL]	14.1	15.4	-0.614	0.539
	Hematocrit [%]	41.8	44.7	-0.307	0.759
	Platelet [10^3/uL]	220	222	-0.036	0.971
	Mean platelet volume [fL]	9.70	9.35	-1.688	0.091
	Neutrophil [10^3/uL]	4.20	4.45	-0.388	0.698
	Lymphocyte [10^3/uL]	1.70	2.05	-0.959	0.338
	Neutrophil / Lymphocyte [%]	0.45	0.50	-0.731	0.465

this result. On the other hand, according to Wiersinga et al., most cohort studies found that approximately 60% of patients were male [9]. However, in another study, an approximately 1:1 ratio of male (50.7%) and female COVID-19 patients was found [15]. In this context, it cannot be said that gender has a direct risk factor for developing the disease. Besides this, the authors did not find any significant difference between the groups in terms of gender.

It was found that the total healthcare workers' median age was 33 ± 8.44 years (min = 20, max = 57). Previous studies found that the total infected healthcare workers' median age was lower than hospitalized workers and the whole population. Mani et al. found that the median age of positive employees was 40 years [19]. In another study, the patients were between 23 and 63 years old, and the median age was 35 years [16]. However, the median age of hospitalized healthcare workers was 49 years [17]. On the other hand, Wiersinga et al. made a review of some studies related to COVID-19. They found that the median age of hospitalized patients among the general population was between 47 and 73 years. They also found that 74% to 86% of these patients were over the age of 50 [9]. Another study examining all hospitalizations within a certain period found the median age to be 57 [18]. In light of this information, it is seen that the average age of healthcare workers is lower compared to the general population.

In the study, only fourteen HCWs received inpatient treatment; the others were followed at their home. The number of hospitalization between the groups was higher in the pneumonia group (n: 11) than in the uncomplicated group (n: 3) (38% *vs.* 6%; $p < 0.001$). Hospitalization time varies in different studies. While Kambhampati et al. found that the median length of hospitalization among healthcare workers with COVID-19 was 4 days (IQR = 3–9 days) [17], Liu et al. found 12.5 days [16]. According to Sahu et al., the incidence of severe disease in health care workers (9.9%) was significantly lower than its incidence among all COVID-19 positive patients (29.4%). They also found that the mortality rate in healthcare workers was meagre (0.3%). Compared to all patients' mortality, this rate is lower than the general population (2.3%). In the study, it is stated that this situation can be explained by the fact that healthcare workers are younger and have less comorbidity compared to the whole society. Besides, the early access of healthcare workers to the health system and better knowledge of the disease process has a positive effect [20]. However, in another study, a substantial proportion of HCWs with COVID-19 had indicators of severe disease. 27.5% of them were admitted to an intensive care unit, 15.8% required invasive mechanical ventilation, and 4.2% died during hospitalization [17]. In the presented study, it was found that healthcare workers were at young ages in general, and only 20.3% of employees had a chronic disease, which can support this study's results. In a study that looks at this situation from another perspective, the authors claimed that because the number of healthcare workers diagnosed with or died because of COVID-19 is not systematically reported, the real impact of the disease on healthcare workers in a global context is unknown [21]. It will also be useful to consider this discourse.

In the presented study, the distribution of employees in the groups was examined in terms of the units they work in. The ratio of employees working in the high-risk units in the uncomplicated group was approximately 1:1, while 3/4 of the pneumonia group employees were working in the high-risk units. As a result of the analysis, the authors found a significantly important difference in the employees' clinical conditions according to the unit they worked in ($p = 0.019$). Workers working in the frontline are thought to be more likely to become infected. In this context, Mani et al. found that 65.4% of positive test results were from frontline healthcare workers.[19] In another study, more than two-thirds (67.4%) of healthcare workers hospitalized with COVID-19 had worked with direct patient contact [17]. On the other hand, in another study among the affected health care workers, they found that many infected workers (77.5%) worked at general wards, and only 22.5% worked in the emergency department and ICU (17.5% and 5%, respectively) [1]. Also, the authors found that there was no statistically significant difference in the proportion of COVID-19 positive PCR detection between healthcare workers from high-risk areas involved in close contact with COVID-19 patients in comparison with clerical, administrative, or laboratory personnel without direct contact with patients [22].

No significant difference between the groups in terms of occupation ($p > 0.05$) was found. However, nurses were the most affected professionals (36.7%). Similarly, some other studies found that nurses were more affected workers among all workers. Kambhampati et al. found the proportion of nursing-related professions among hospitalized healthcare workers to be 36.3% [17]. In another study, 67% of those infected healthcare workers consisted of nurses [16]. These results may be explained by the fact that nurses have the highest number of occupational groups in hospitals.

The comorbidity rate was 20.3% in the presented study, and the most common chronic diseases were hypertension, asthma, and diabetes mellitus. The authors did not find a significant relationship between the prognosis of COVID-19 and any of the chronic diseases ($p > 0.05$). Similar to the presented study, Liu et al. found that the number of employees with one or more comorbidities was low (13%) [16]. These were listed as hypertension, uterine fibroids, diabetes, depressive disorder, thyroid nodules, or abdominal lymphatic tuberculosis according to their prevalence. In the study of Zhang et al., hypertension (30.0%) and diabetes mellitus (12.1%) were the most common comorbidities [18]. Additionally, they found that the chronic obstructive pulmonary disease rate was low (1.4%). On the other hand, according to Kambhampati et al., 89.8% of the workers had at least one underlying medical condition. They found that obesity was the most commonly reported disease (72.5%), hypertension (40.6%), and diabetes (30.9%) were the other common diseases [17]. The low number of comorbidity in the presented study can be explained by the employees' low age. On the other hand, the fact that hypertension and diabetes were the most common chronic diseases can be explained by that they have a high prevalence in our population [23].

It was found that the most common onset symptoms were sore throat, cough, malaise/weakness/fatigue, shortness of breath, and fever. On the other hand, stinging in breathing and dysuria were very rare. Symptoms of the disease did not differ according to the severity of the disease. None of the signs & symptoms had a significantly important difference between the groups ($p > 0.05$). In many studies, the most common clinical symptoms were fever, cough, fatigue [9, 10, 16–19, 24]. Also, it was found that shortness of breath [17], and headache (59.5%), muscle aches (54.1%), sore throat (50.8%) were other common symptoms [19]. On the other hand, myalgia, dyspnoea, headache, dizziness, abdominal pain, diarrhoea, nausea, loss of appetite, difficulty breathing or chest tightness, chill, chest pain, and vomiting were less common symptoms [9, 10, 16, 18, 24]. Although the cause is not known precisely, it is known that the intestinal flora may change in COVID-19 patients [25]. Zhang et al. found that gastrointestinal symptoms were 39.6% among patients [18]. Another study had 15%–39% nausea/vomiting or diarrhoea symptoms [9]. However, according to Cetintepe and Ilhan, diarrhoea (3.7%) and vomiting (5.0%) are less common symptoms [10]. In a different study, 10.1% of the patients experienced diarrhoea and nausea 1 to 2 days before developing fever and dyspnoea [1]. Therefore, healthcare professionals need to consider these rare symptoms as well.

According to Wiersinga et al., the common laboratory abnormalities in hospitalized patients include lymphopenia, elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumour necrosis factor-*a*, IL-1, IL-6), and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer, low fibrinogen) [9]. In another study, the blood counts of 17% of cases showed leukocytopenia, and only 2% showed leukocytosis on admission; 34% of the patients presented with lymphocytopenia and 11% presented thrombocytopenia. Elevated C-reactive protein and amyloid A levels were presented in 45% and 59% of cases, respectively. Elevated levels of alanine aminotransferase and aspartate aminotransferase were less common. Only 3% of cases had abnormal procalcitonin serum levels. Notably, 47 (80%) of cases had high levels of IL-6. However, most patients demonstrated normal levels of D-dimer, creatinine, and creatine kinase [16]. Zhang et al. investigated the patients into two groups (non-severe and severe). In their study, lymphopenia and eosinopenia were observed in most patients. Blood eosinophil counts correlate positively with lymphocyte counts in severe and non-severe patients after hospital

admission. Significantly higher D-dimer levels, C-reactive protein, and procalcitonin were associated with severe patients compared to non-severe patients. More comorbidities, higher median values of leukocyte count, D-dimer, CRP, PCT, and lower lymphocyte percentage were found in severe cases, compared to non-severe cases. No difference was identified for the occurrence rates of most signs and symptoms between non-severe and severe patients [18]. In the presented study, the authors investigated albumin, direct bilirubin, C-reactive protein, D-dimer, white blood cells, red blood cells, haemoglobin, hematocrit, platelet, mean platelet volume, neutrophil, lymphocyte levels. Opposite of the previous studies, they did not find any significant high levels of these blood parameters. There was no significant relationship between the groups regarding their blood test results ($p > 0.05$). In the authors' opinion, this result may be explained by none of the workers stayed in the intensive care unit, and also, there was not any death result in their study.

Conclusion

COVID-19 is a highly contagious pandemic that the whole world has been struggling with for the last year. Healthcare workers are in the risk group for COVID-19 disease. HCWs working in high-risk units are more vulnerable. Identifying early symptoms and defining more vulnerable groups will help protect workers from disease.

Limitations of the study

This study has some limitations. First, this study was conducted with only 79 healthcare professionals who confirmed COVID-19 from a single hospital in Istanbul. Therefore, it can not be generalized for all healthcare professionals. Second, since it is a retrospective study, there was limited access to some data. More detailed data required for the study (e.g. employees' weight, smoking status, etc.) were not available at the analysis time. Thus, the study provides only a preliminary overview of a group of healthcare workers' epidemiological characteristics and clinical outcomes. More research is needed on this subject.

Conflict of interest: *The authors declare that there is no conflict of interests regarding the publication of this paper.*

References

1. Wang D, Hu Bo, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061–1069, doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
2. Salazar de Pablo G, Vaquerizo-Serrano J, Catalan A, et al. Impact of coronavirus syndromes on physical and mental health of health care workers: Systematic review and meta-analysis. J Affect Disord. 2020; 275: 48–57, doi: 10.1016/j.jad.2020.06.022, indexed in Pubmed: 32658823.
3. https://covid19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html (23.10.2020).
4. ICN-The International Council of Nurses. October 28 2020. https://www.icn.ch/news/icn-confirms-1500-nurses-have-died-covid-19-44-countries-and-estimates-healthcare-worker-covid (24.12.2020).
5. Long C, Xu H, Shen Q, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020; 126: 108961, doi: 10.1016/j.ejrad.2020.108961, indexed in Pubmed: 32229322.
6. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020; 296(2): E32–E40, doi: 10.1148/radiol.2020200642, indexed in Pubmed: 32101510.
7. Bai HX, Hsieh B, Xiong Z, et al. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. Radiology. 2020; 296(2): E46–E54, doi: 10.1148/radiol.2020200823, indexed in Pubmed: 32155105.
8. https://www.who.int/health-topics/coronavirus#tab=tab_1 (23.10.2020).
9. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020; 324(8): 782–793, doi: 10.1001/jama.2020.12839, indexed in Pubmed: 32648899.
10. Cetintepe S, Ilhan M. COVİD-19 Salgınında Sağlık Çalışanlarında Risk Azaltılması. Journal of Biotechnology and Strategic Health Research. 2020, doi: 10.34084/bshr.712539.
11. COVID-19 (SARS-CoV-2 Enfeksiyonu) Genel Bilgiler, Epidemioloji ve Tanı. https://covid19.saglik.gov.tr/Eklenti/39060/0/covid-19rehberigenelbilgilerepidemiyolojivetanipdf.pdf (23.10.2020).
12. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections - the state of the art. Emerg Microbes Infect. 2020; 9(1): 747–756, doi: 10.1080/22221751.2020.1745095, indexed in Pubmed: 32196430.
13. Chu J, Yang N, Wei Y, et al. Clinical characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China. J Med Virol. 2020; 92(7): 807–813, doi: 10.1002/jmv.25793, indexed in Pubmed: 32222986.
14. Amnesty International. Global: Amnesty analysis reveals over 7,000 health workers have died from COVID-19. https://www.amnesty.org/en/latest/news/2020/09/amnesty-analysis-7000-health-workers-have-died-from-covid19/ (23.10.2020).
15. T.C. Sağlık Bakanlığı. COVID-19 (SARS-CoV-2 Enfeksiyonu) Erişkin Hasta Tedavisi Bilimsel Danışma Kurulu Çalışması. https://covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html (22.10.2020).
16. Liu J, Ouyang L, Guo Pi, et al. Epidemiological, Clinical Characteristics and Outcome of Medical Staff Infected with COVID-19 in Wuhan, China: A Retrospective Case Series Analysis. , doi: 10.1101/2020.03.09.20033118.
17. Kambhampati A, O'Halloran A, Whitaker M, et al. COVID-19–Associated Hospitalizations Among Health Care Personnel — COVID-NET, 13 States, March 1–May 31, 2020. MMWR. Morbidity and Mortality Weekly Report. 2020; 69(43): 1576–1583, doi: 10.15585/mmwr.mm6943e3.
18. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75(7): 1730–1741, doi: 10.1111/all.14238, indexed in Pubmed: 32077115.
19. Mani NS, Budak JZ, Lan KF, et al. Prevalence of COVID-19 Infection and Outcomes Among Symptomatic Healthcare Workers in Seattle, Washington. Clin Infect Dis. 2020 [Epub ahead of print], doi: 10.1093/cid/ciaa761, indexed in Pubmed: 32548613.
20. Sahu AK, Amrithanand VT, Mathew R, et al. COVID-19 in health care workers - A systematic review and meta-analysis. Am J Emerg Med. 2020; 38(9): 1727–1731, doi: 10.1016/j.ajem.2020.05.113, indexed in Pubmed: 32738467.
21. PALA SÇ, METİNTAS S. COVID-19 Pandemisinde Sağlık Çalışanları. Eskişehir Türk Dünyası Uygulama ve Araştırma Merkezi Halk Sağlığı Dergisi. 2020, doi: 10.35232/estudamhsd.789806.
22. Folgueira M, Muñoz-Ruipérez C, Alonso-López M, et al. SARS-CoV-2 infection in Health Care Workers in a large public hospital in Madrid, Spain, during March 2020. , doi: 10.1101/2020.04.07.20055723.
23. Satman İ, Alagöl F, Ömer B, et al. Türkiye Diyabet, Hipertansiyon, Obezite ve Endokrinolojik hastalıklar prevalans çalışması-II 2010.
24. Wang X, Liu W, Zhao J, et al. Clinical characteristics of 80 hospitalized frontline medical workers infected with COVID-19 in Wuhan, China. J Hosp Infect. 2020 [Epub ahead of print], doi: 10.1016/j.jhin.2020.04.019, indexed in Pubmed: 32302722.
25. Perisetti A, Gajendran M, Goyal H. Putative Mechanisms of Diarrhea in COVID-19. Clin Gastroenterol Hepatol. 2020; 18(13): 3054–3055, doi: 10.1016/j.cgh.2020.06.008, indexed in Pubmed: 32535231.

VIA MEDICA

ORIGINAL ARTICLE

Piotr Lackowski[1], Maciej Piasecki[1], Michał Kasprzak[1], Jacek Kryś[2], Piotr Niezgoda[1], Jacek Kubica[1]

[1]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Dr A. Jurasz University Hospital no. 1, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

COVID-19 pandemic year in the cardiology department

Corresponding author:

Piotr Lackowski, Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Marii Skłodowskiej-Curie 9 St., 85-094 Bydgoszcz, Poland, e-mail: lackowski.piotr@gmail.com

Medical Research Journal 2021; Volume 6, Number 1, 40–46
10.5603/MRJ.a2021.0009

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: A COVID-19 pandemic has resulted in noticeable changes in the functioning of the Department of Cardiology, dr A. Jurasz University Hospital no. 1 in Bydgoszcz. This study aims to compare the functioning of the university cardiology department in the pandemic year 2020 to the previous years.

Materials and methods: The retrospective analysis of patients hospitalized in the Department of Cardiology, dr A. Jurasz University Hospital no 1 in Bydgoszcz, Poland, has been performed. Collected data included the number of patients admitted to the hospital, medical diagnoses, performed procedures and in-hospital mortality.

Results: Throughout 2020 numbers of both new hospitalizations and diagnostic or therapeutic procedures in electrophysiology, echocardiography and invasive cardiology showed a major decrease. The greatest impact was observed in March, April, and the last 3 months of the year. The pandemic also affected in-hospital mortality.

Conclusions: The observed decrease in the number of hospital admissions of specialized cardiac procedures performed in 2020 may have a serious impact on future patients' profile.

Key words: COVID-19, SARS-CoV-2, pandemics, cardiology, hospitals

Med Res J 2021; 6 (1): 40–46

Introduction

A Coronavirus Disease 2019 (COVID-19) pandemic that has lasted since the beginning of the year 2020 caused a change in many areas of life for people from all over the world. The increasing number of patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) affected also the Polish healthcare system triggering major changes in patients' habits. Despite the initially limited number of infected patients, the snowballing number of new positive SARS CoV-2 cases caused also in the department of cardiology the necessity to cope with a new medical issue and forced opening the insulation section for the COVID-19 patients. This study aims to compare the functioning of the university cardiology department in the pandemic year 2020 to the previous years.

Materials and methods

The data was obtained from the electronic database used in the Department of Cardiology, dr A. Jurasz University Hospital no 1 in Bydgoszcz. Retrospective analysis of patients' medical history collected by attending physicians enabled them to obtain information regarding the number of patients admitted to the hospital, medical diagnoses, performed procedures and in-hospital mortality. The data on procedures performed in 2020 were compared to the period of 2018–2019, whereas comparison of data on medical diagnoses, number of patients and mortality included 2020 versus 2016–2019 period. The data regarding new hospitalizations included both new admissions to the hospital and transfers from other departments. The ratio of the number of deaths to the sum of all patients discharged from the department was used to determine the in-hospital mortality. The number of implanted or replaced cardioverter-defibrillators included data on single and dual-chamber defibrillators, subcutaneous devices and cardiac resynchronization therapy defibrillators. The number of implanted and replaced pacemakers included data on single and dual-chamber devices, as well as cardiac resynchronization pacemakers. Publicly available internet data on the number of new cases was used to refer observed frequency of analysed events

to the incidence of COVID-19 in Poland and the in the Kuyavian-Pomeranian Voivodeship, where dr A. Jurasz University Hospital no. 1 is located. The statistical analysis was carried out using the Statistica 13.0 package (TIBCO Software Inc, California, USA). Data regarding each year were presented as monthly or weekly averages (means) with standard deviations. The Shapiro-Wilk test demonstrated the non-normal distribution of the investigated variables. Therefore, a non-parametric test was used for statistical analysis. Comparisons between the year 2020 and previous years were performed with the Mann-Whitney unpaired rank-sum test. Results were considered significant at $p < 0.05$.

Results

First reports of patients infected with SARS-CoV-2 spread in December 2019. The first patient in Poland was identified on 4th March 2020 – in the hospital in Zielona Gora. Called by the World Health Organization (WHO) COVID-19 pandemic affected also the functioning of the Department of Cardiology, dr A. Jurasz University Hospital No. 1 in Bydgoszcz. The incidence of COVID-19 in the Kuyavian-Pomeranian Voivodeship, where dr A. Jurasz University Hospital no. 1 is located, were higher than in Poland as a whole country in the last four months of 2020 (Fig. 1).

The pandemic itself imposed major changes in the functioning of the Department of Cardiology, dr A. Jurasz University Hospital No. 1 in Bydgoszcz. In the first half of March, clinical classes for students were cancelled. The temporary change of work organization of the medical staff to working in teams lasted until the beginning of May. The increase in the number of infected patients in the last three months of the year 2020 affected functioning again. On November 9th, the isolation section for patients infected with COVID-19 was opened in the study clinic - initially for 6 patients and then extended to 15 afterwards. Taken actions resulted in a reduction of new hospitalizations (3396 patients in 2020 compared to 3906 in 2019) (Fig. 2) The number of primary diagnoses among discharged patients also changed (Fig. 3).

The collected data showed an increase in mortality in 2020 in comparison to the previous period (Fig. 4). The increase was seen in the months of the first and second waves of the COVID 19 pandemic. The data collected from the study department is consistent with the data recorded in the Polish Registry of Civil Status. (Fig. 5).

The change was also seen in the number of procedures performed in the field of electrophysiology, echocardiography and invasive cardiology (Tab. 1). The differences were observed in the following procedures: transthoracic echocardiographies, implanted and replaced Cardioverter-defibrillators (ICDs), left atrial appendage occlusions and intravascular ultrasound measurements (only procedure with an increase in the number of procedures).

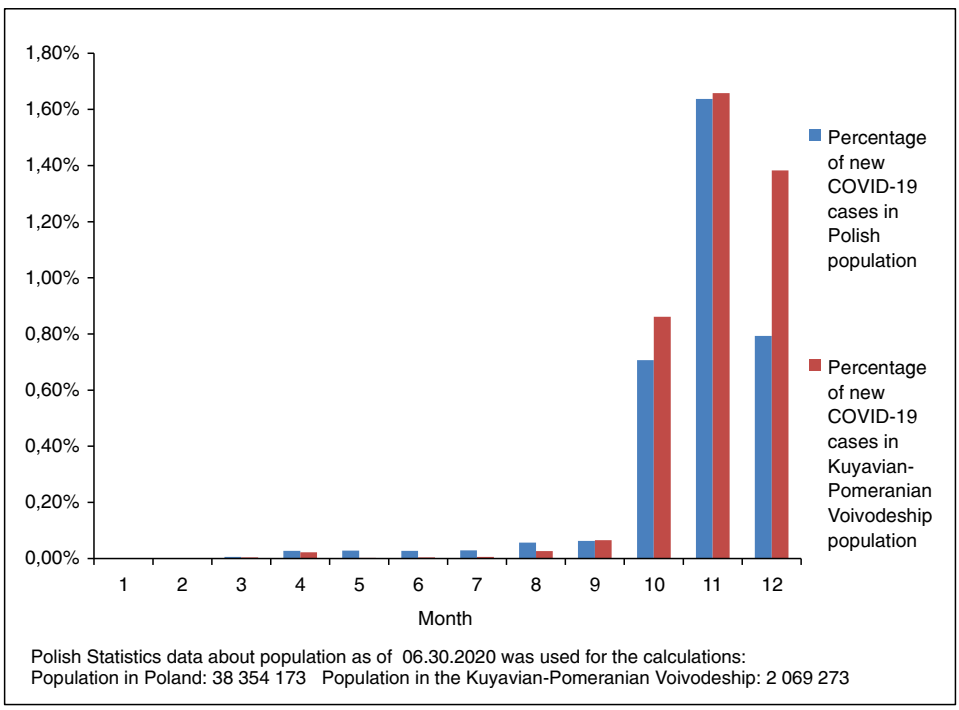
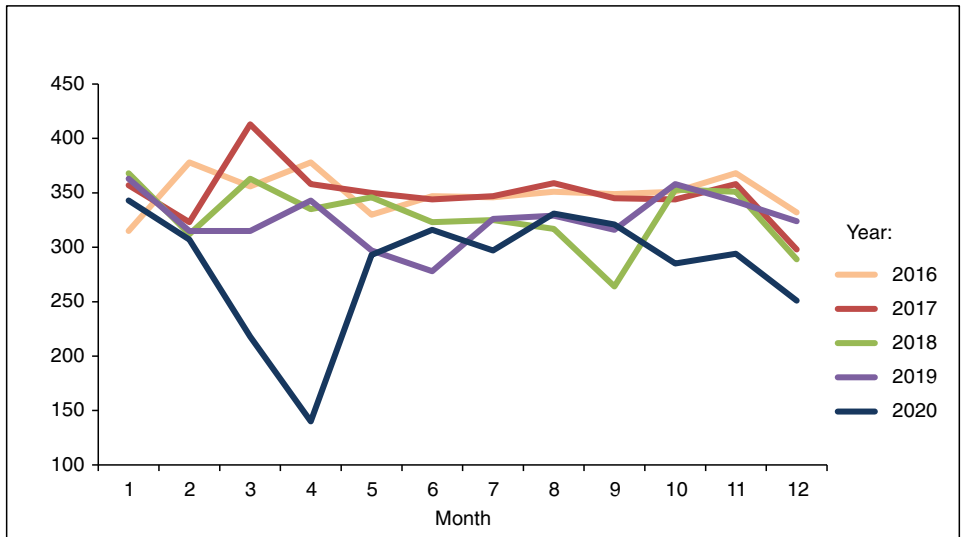


Figure 1. Incidence of COVID-19 in 2020



Year:	2016	2017	2018	2019	2020
Sum:	4201	4196	3946	3906	3396
Monthly average:	350,08	349,67	328,83	325,50	283,00
Standard deviation:	18,84	26,57	30,71	24,19	56,51
P-value:	p=0,0002	p=0,0002	p=0,0141	p=0,0281	

Figure 2. Number of new hospitalizations in the department of cardiology, dr A. Jurasz University Hospital No. 1 in Bydgoszcz

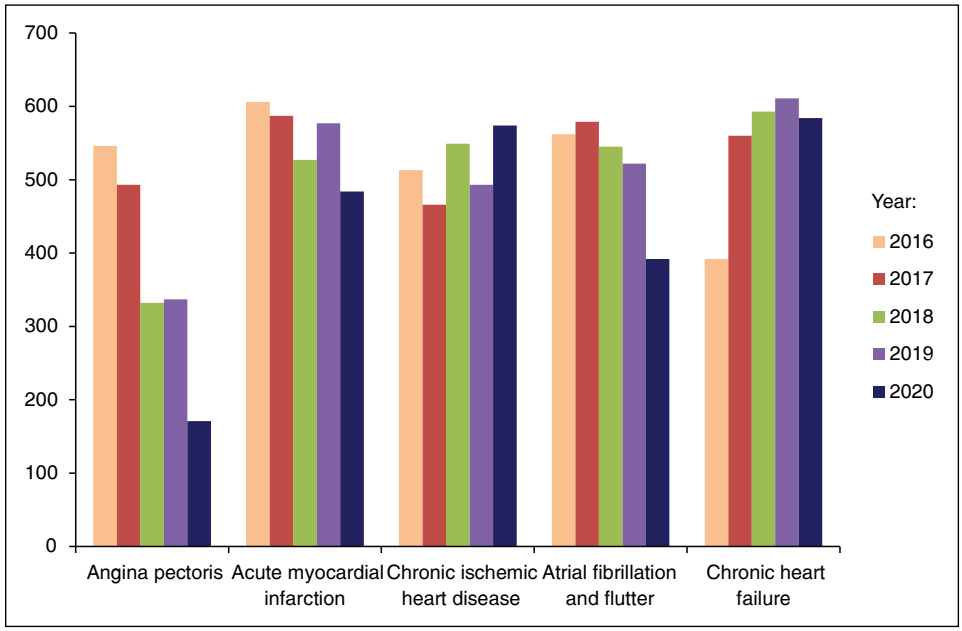
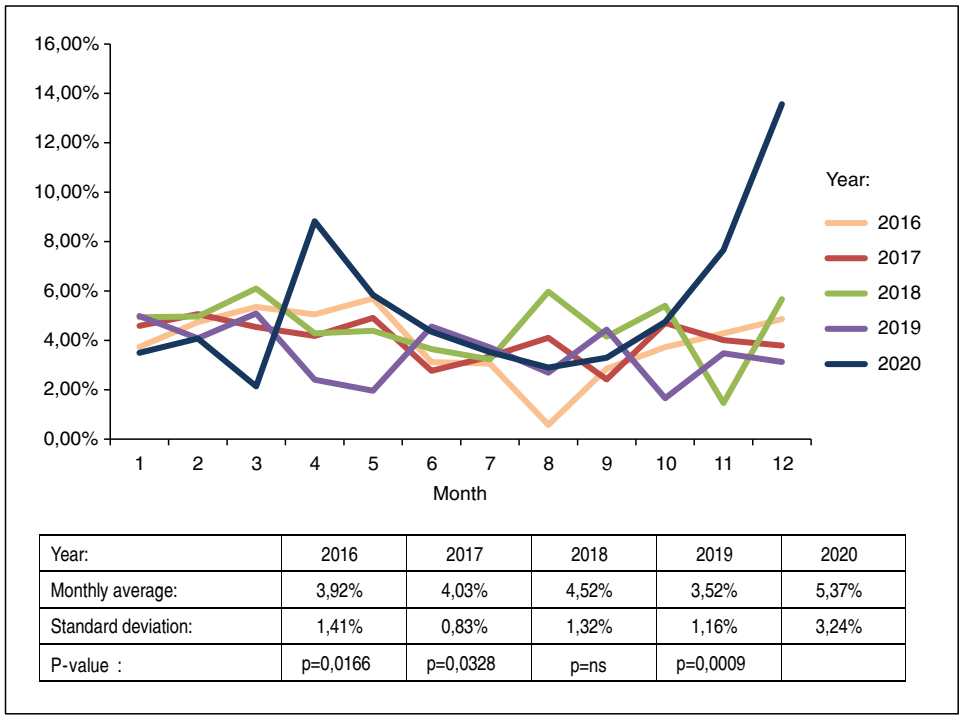
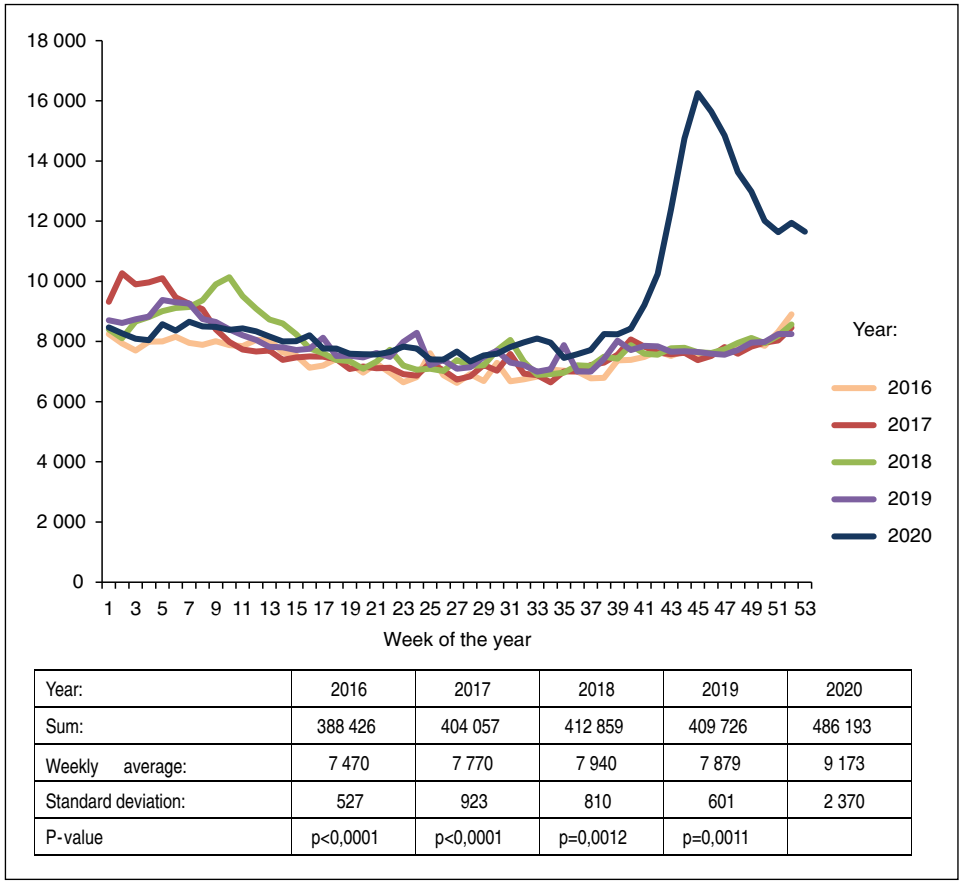


Figure 3. Number of primary diagnoses among patients discharged from the department of cardiology, dr A. Jurasz University Hospital No. 1 in Bydgoszcz



Year:	2016	2017	2018	2019	2020
Monthly average:	3,92%	4,03%	4,52%	3,52%	5,37%
Standard deviation:	1,41%	0,83%	1,32%	1,16%	3,24%
P-value :	p=0,0166	p=0,0328	p=ns	p=0,0009	

Figure 4. The mortality rate in the department of cardiology, dr A. Jurasz University Hospital No. 1 in Bydgoszcz



Year:	2016	2017	2018	2019	2020
Sum:	388 426	404 057	412 859	409 726	486 193
Weekly average:	7 470	7 770	7 940	7 879	9 173
Standard deviation:	527	923	810	601	2 370
P-value	p<0,0001	p<0,0001	p=0,0012	p=0,0011	

Figure 5. Number of deaths registered in the Polish Registry of Civil Status

Table 1. A detailed list of the monthly number of procedures performed in the department of cardiology, dr A. Jurasz University Hospital no. 1 in Bydgoszcz

Type of procedure	Year	Month												Sum	Monthly average	Standard deviation	P-value
		1	2	3	4	5	6	7	8	9	10	11	12				
Number of performed Transthoracic Echocardiographies	2018	307	226	301	261	308	296	299	279	220	345	308	262	3412	284,33	36,38	P = ns
	2019	317	290	269	328	263	268	316	310	295	325	310	330	3621	301,75	24,30	P = 0,0016
	2020	299	267	224	130	243	283	283	262	293	246	267	251	3048	254,00	44,82	
Number of performed Transesophageal Echocardiographies	2018	33	15	45	42	43	41	40	28	30	48	53	33	451	37,58	10,31	P = ns
	2019	32	32	31	27	23	38	32	49	43	38	55	45	445	37,08	9,42	P = ns
	2020	33	32	23	2	17	40	39	39	46	39	23	11	344	28,67	13,49	
Number of implanted and replaced Cardioverter-defibrillators	2018	14	14	13	8	9	12	9	14	13	21	13	8	148	12,33	3,63	P = ns
	2019	14	14	14	10	9	16	20	13	17	17	19	21	184	15,33	3,73	P = 0,0250
	2020	12	13	11	9	13	16	12	14	14	13	12	10	149	12,42	1,88	
Number of implanted and replaced Pacemakers	2018	17	11	14	15	17	12	14	17	9	11	9	14	160	13,33	2,93	P = ns
	2019	20	11	17	17	11	13	12	17	11	12	17	9	167	13,92	3,48	P = ns
	2020	9	14	13	5	19	15	15	14	19	22	8	7	160	13,33	5,25	
Number of performed Cardiac ablations	2018	18	13	20	18	18	14	12	17	5	20	21	12	188	15,67	4,62	P = ns
	2019	14	20	13	19	11	17	17	22	16	19	32	20	220	18,33	5,37	P = ns
	2020	15	18	10	3	17	20	12	20	20	9	12	6	162	13,50	5,76	
Number of performed coronary angiographies	2018	135	104	141	131	122	120	121	131	106	115	139	107	1472	122,67	12,91	P = ns
	2019	141	107	127	135	139	94	138	130	133	154	124	125	1547	128,92	15,83	P = ns
	2020	135	123	101	69	131	154	140	133	148	128	117	105	1484	123,67	23,28	
Number of performed percutaneous coronary interventions	2018	95	66	86	72	92	86	49	72	61	69	97	67	912	76	15,00	P = ns
	2019	96	68	80	71	88	64	117	83	102	110	81	85	1045	87,08	16,48	P = ns
	2020	79	70	72	41	85	101	92	80	91	97	67	78	953	79,42	16,17	
Number of performed Left Atrial appendage occlusions	2018	5	4	6	8	8	2	5	1	4	4	6	1	54	4,5	2,35	P = 0,0475
	2019	3	1	5	1	2	4	2	2	3	5	4	2	34	2,83	1,40	P = ns
	2020	4	2	2	0	1	7	0	4	5	2	3	0	30	2,5	2,20	

↓

Table 1 cont. A detailed list of the monthly number of procedures performed in the department of cardiology, dr A. Jurasz University Hospital no. 1 in Bydgoszcz

Type of procedure	Year	Month												Sum	Monthly average	Standard deviation	P-value
		1	2	3	4	5	6	7	8	9	10	11	12				
Number of performed MitraClip procedures	2018	0	1	1	1	0	1	2	0	1	3	3	3	16	1,33	1,15	P = ns
	2019	1	0	2	1	2	1	2	5	5	2	2	2	25	2,08	1,51	P = ns
	2020	1	1	0	0	1	2	2	3	2	2	2	2	18	1,5	0,90	
Number of performed fractional flow reserve measurements	2018	18	12	19	13	13	10	15	16	17	11	24	16	184	15,33	3,92	P = ns
	2019	14	11	10	13	14	11	16	13	12	14	19	21	168	14	3,28	P = ns
	2020	28	26	12	4	35	17	18	25	21	21	10	3	220	18,33	9,73	
Number of performed intravascular ultrasound measurements	2018	0	0	1	0	0	2	0	0	1	0	0	0	4	0,33	0,65	P = 0,0002
	2019	1	0	2	1	0	3	3	0	2	0	1	1	14	1,17	1,11	P = 0,0074
	2020	3	4	2	1	4	5	3	3	3	5	2	0	35	2,92	1,51	

Discussion

Our study shows the significant increase in mortality rate in 2020 in comparison with previous analysed years with two most pronounced peaks in April and December which can be explained by the outburst of two waves of COVID-19 pandemic. Data on peaks of the mortality rate in the Department of Cardiology is consistent with the country-wide reports obtained from The Polish Registry of Civil Status. Taking into account the procedures performed throughout 2020, significance was reached in differences in numbers of transthoracic echocardiographies, implanted ICDs and left atrial appendage occlusions. Other differences observed in the performed analysis were only numerical. The significant increase in the rate of intravascular ultrasound, in turn, may be explained by better accessibility of the procedure as a result of its recent reimbursement by the National Health Fund and it should not be correlated to the COVID pandemic

The COVID 19 pandemic affected also the total number of hospitalized patients in the study Clinic. Similar results were observed by Fersia et all. The authors observed a significant decrease in both hospital admissions and performed procedures in the Cardiology Department at Dumfries and Galloway Royal Infirmary [1]. A study by Roffi et al. also showed that the COVID 19 pandemic significantly reduced the number of invasive procedures. The decrease was the grater the less urgent the procedure was [2]. The impact of COVID-19 on cardiac patients was similarly presented by DeFilippis et al. The reorganization of health care structures spurred by the COVID-19 pandemic has significantly affected patients with heart failure, with increased access to telemedicine and cancellation of elective diagnostic and therapeutic procedures [3]. Harky et al. showed that elective coronary treatments and imaging have been largely cancelled across the world to make way for increased resources for COVID-19 patients. Also, the number of hospital patients presenting with coronary symptoms during the outbreak has decreased internationally [4]. Metzler et al. also showed a decline in admissions for percutaneous coronary intervention. The authors estimated that 275 patients were not treated in March and that 110 acute coronary syndrome deaths occurred during this timeframe [5]. The pandemic imposed major changes widely around the world. A review done by Tam et al., showed a significant increase in admission time to a hospital in Hong Kong [6], whereas Baldi et al. showed that the COVID-19 pandemic is significantly correlated to the increase of out of hospital cardiac arrest in Italy [7].

It is worth mentioning that the Department of Cardiology, dr A. Jurasz University Hospital no. 1 in

Bydgoszcz is conducting the ReCOVery-SIRIO Clinical Trial (EudraCT Number: 2020-001951-42), aiming to evaluate the effect of drugs commonly used in cardiology, amiodarone and verapamil on the clinical course of COVID-19. At the time of publication, the study is in progress.

Conclusions

COVID-19 pandemic resulted in functioning changes and an increase of in-hospital mortality in the Department of Cardiology, dr A. Jurasz University Hospital no. 1 in Bydgoszcz. The observed decrease in the number of hospital admissions and specialized cardiac procedures performed in 2020 may have a serious impact on future patients' profile.

Statement of competing interests: *All of the authors declare that they are employees of the hospital which is the subject of the article.*

References

1. Fersia O, Bryant S, Nicholson R, et al. The impact of the COVID-19 pandemic on cardiology services. Open Heart. 2020; 7(2), doi: 10.1136/openhrt-2020-001359, indexed in Pubmed: 32855212.
2. Roffi M, Capodanno D, Windecker S, et al. Impact of the COVID-19 pandemic on interventional cardiology practice: results of the EAPCI survey. EuroIntervention. 2020; 16(3): 247–250, doi: 10.4244/EIJ-D-20-00528, indexed in Pubmed: 32490825.
3. DeFilippis EM, Reza N, Donald E, et al. Considerations for Heart Failure Care During the COVID-19 Pandemic. JACC Heart Fail. 2020; 8(8): 681–691, doi: 10.1016/j.jchf.2020.05.006, indexed in Pubmed: 32493638.
4. Harky A, Chor CY, Khare Y. COVID-19 and its impact on cardiology service. Acta Biomed. 2020; 91(4): ahead of print, doi: 10.23750/abm.v91i4.9828, indexed in Pubmed: 33525237.
5. Metzler B, Siostrzonek P, Binder RK, et al. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J. 2020; 41(19): 1852–1853, doi: 10.1093/eurheartj/ehaa314, indexed in Pubmed: 32297932.
6. Tam CCF, Cheung KS, Lam S, et al. Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment-Elevation Myocardial Infarction Care in Hong Kong, China. Circ Cardiovasc Qual Outcomes. 2020; 13(4): e006631–E197, doi: 10.1161/CIRCOUTCOMES.120.006631, indexed in Pubmed: 32182131.
7. Baldi E, Sechi GM, Mare C, et al. Lombardia CARe researchers. COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests. Eur Heart J. 2020; 41(32): 3045–3054, doi: 10.1093/eurheartj/ehaa508, indexed in Pubmed: 32562486.

VIA MEDICA

ORIGINAL ARTICLE

Klaudyna Grzelakowska[1], Jacek Kryś[2]

[1]Faculty of Medicine, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland
[2]Antoni Jurasz University Hospital No. 1., Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland

The impact of COVID-19 on healthcare workers' absenteeism: infections, quarantines, sick leave — a database analysis of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz, Poland

Corresponding author:

Klaudyna Grzelakowska, Faculty of Medicine, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland,
e-mail: klaudyna.grzelakowska@gmail.com

Medical Research Journal 2021; Volume 6, Number 1, 47–52
10.5603/MRJ.a2021.0012

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: The COVID-19 pandemic through its impact on healthcare workers (HCWs) could result in possible disturbances in the stability of providing medical services. This paper aimed to analyse the influence of the SARS-CoV-2 pandemic on HCWs regarding their absenteeism and availability to work.

Materials and methods: An analysis of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz database was conducted regarding the number of SARS-CoV-2 infections and quarantines of HCWs and the number of HCWs on sick leave for the period between the 1st of October 2020 and the 28th of February 2021. The population was analysed regarding occupational groups (doctors, nurses, administrative and technical workers, other medical staff members) and in the context of regional epidemiological trends.

Results: Infection and quarantine rates were higher in HCWs than in the general population with nurses and doctors being the most affected groups. A significant increase in the number of HCWs on sick leave in 2020/2021 was observed in comparison with 2019/2020.

Conclusions: Healthcare workers are a group significantly affected by the COVID-19 pandemic. The availability of workforce in the hospital has been impacted both directly (infections, quarantines) and indirectly (sick leave). Further studies in the area of HCWs' security are needed.

Key words: SARS-CoV-2, HCW, medical personnel, pandemic, coronavirus

Med Res J 2021; 6 (1): 47–52

Introduction

The first confirmed case of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was reported in Poland on the 4th of March 2020 [1]. Since then, the coronavirus disease 2019 (COVID-19) pandemic has been progressively spreading and affecting almost every area of our lives, especially the aspect of healthcare services. With the shrinking capacities of many hospitals and medical personnel shortages, the issue of healthcare system organization in the face of the pandemic is in the spotlight. At the heart of this global crisis are the healthcare workers (HCWs) fighting an uneven battle with a rapidly spreading viral agent. The epidemiological situation has undoubtedly taken a heavy toll on HCWs in particular. The need for isolation in case of a confirmed SARS-CoV-2 infection as well as compulsory quarantines result in abandonment of work and therefore in possible disturbances in the stability of providing medical services. To maintain a well-functioning healthcare system with continuity of medical services and stability of workforce the issue of COVID-19 in HCWs needs to be properly contained and controlled. However, first and foremost the phenomena need to be better understood. This paper aimed to analyse the influence of the SARS-CoV-2 pandemic on healthcare workers regarding their absenteeism and availability to work in the context of the hospital population itself as well as the general population in the region.

Materials and methods

We have analysed the data acquired from the hospital database of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz, Kuyavian-Pomeranian Voivodeship, Poland. The collected data included the number of HCWs that:

— tested positive for SARS-CoV-2,
— were quarantined,
— went on sick leave.

The data were obtained for each day between the 1st of October 2020 and the 28th of February 2021. Additionally, the number of HCWs that went on sick leave was also analysed for the corresponding period of 2019/2020 (from the 1st of October 2019 to the 29th of February 2020).

The study population comprised of HCWs, the Antoni Jurasz University Hospital No. 1. in Bydgoszcz employees. The acquired data were analysed regarding specific occupational groups: doctors, nurses, administrative and technical workers, other medical staff members. The total number of HCWs in each group was determined for each month separately based on the data acquired from the hospital database.

For a comparison with general epidemiological trends in the region, the official, freely available data was used, provided by the Voivodship Sanitary and Epidemiological Station in Bydgoszcz [2] and the Ministry of Health [3] for the period between the 8th of November 2020 and the 28th of February 2021. The data for the period between the 1st of October 2020 and the 7th of November 2020 was made available by the Voivodship Sanitary and Epidemiological Station in Bydgoszcz upon request. The data pertained to the number of SARS-CoV-2 positive cases as well as the number of people quarantined in the Kuyavian-Pomeranian Voivodeship. The total number of people in the voivodeship used for the analysis was determined based on data of Statistics Poland (Polish: Główny Urząd Statystyczny) to be 2,069,273 [4].

The statistical analysis was performed using Statistica 13.3 software. Wilcoxon signed-rank test was used to evaluate the data. Results were considered significant at $p < 0.05$.

Results

In the period between the 1st of October 2020 and the 28th of February 2021 a total number of 467 cases of a positive SARS-CoV-2 test result were reported among HCWs of Antoni Jurasz University Hospital No. 1. in Bydgoszcz, meaning that almost 1 in 4 HCWs (23.77%) got infected over the analysed period. Among those, there were 89 doctors (27.07%), 229 nurses (31.46%), 37 administrative and technical workers (13.13%) and 112 other medical staff members (17.89%). Statistically significant differences were found between almost all of the occupational groups regarding daily rates of SARS-CoV-2 infections (percentage of HCWs that tested positive for SARS-CoV-2 in accordance to a total number of HCWs in each group per day). The nurses and the doctors had the highest SARS-CoV-2 incidence rate (statistically significant differences between these groups were not found), while the administrative and technical workers and other medical staff members had the lowest rates (statistically significant differences between these groups were not found either). The monthly infection rates of HCWs that tested positive for SARS-CoV-2 in each group are shown in Figure 1.

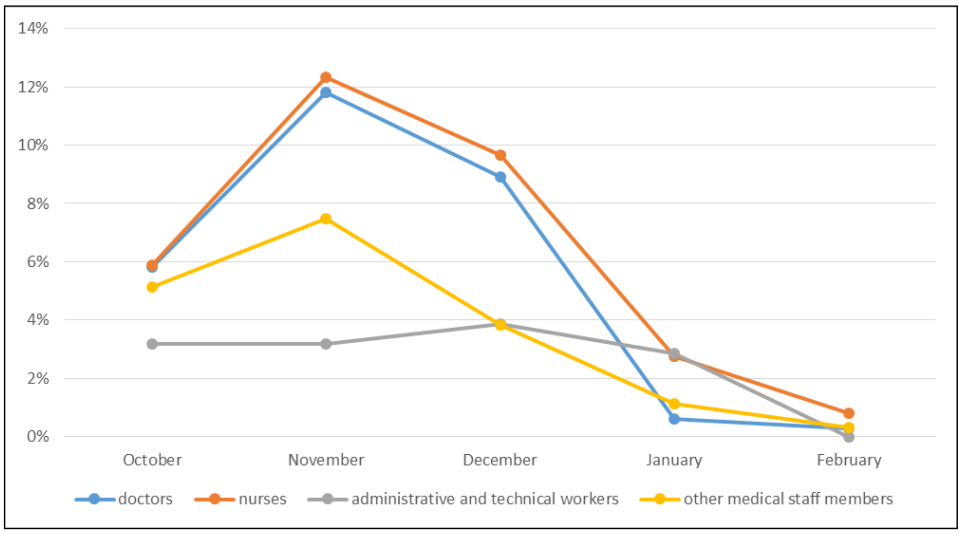


Figure 1. Monthly infection rates in the healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz divided into occupational groups

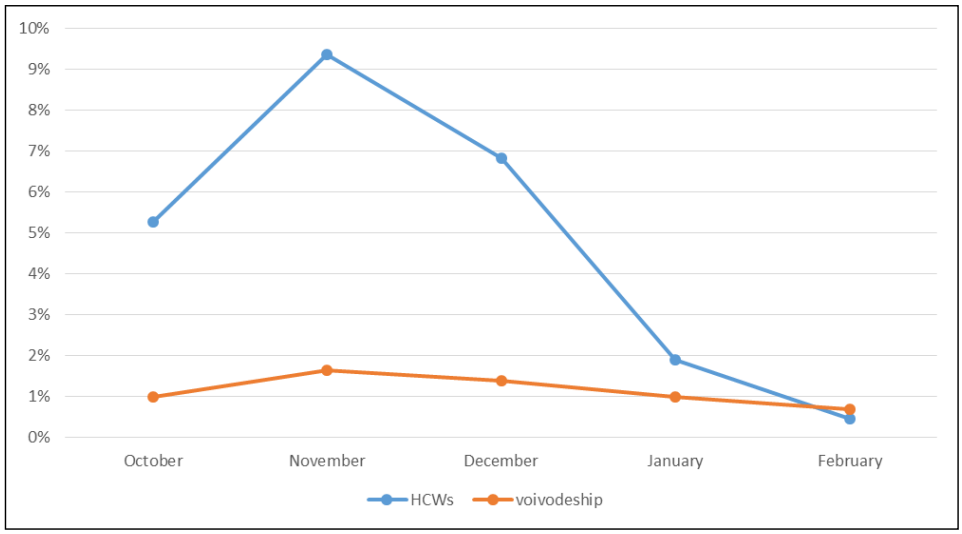


Figure 2. Monthly infection rates in the healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz and the general population of the Kuyavian-Pomeranian Voivodeship

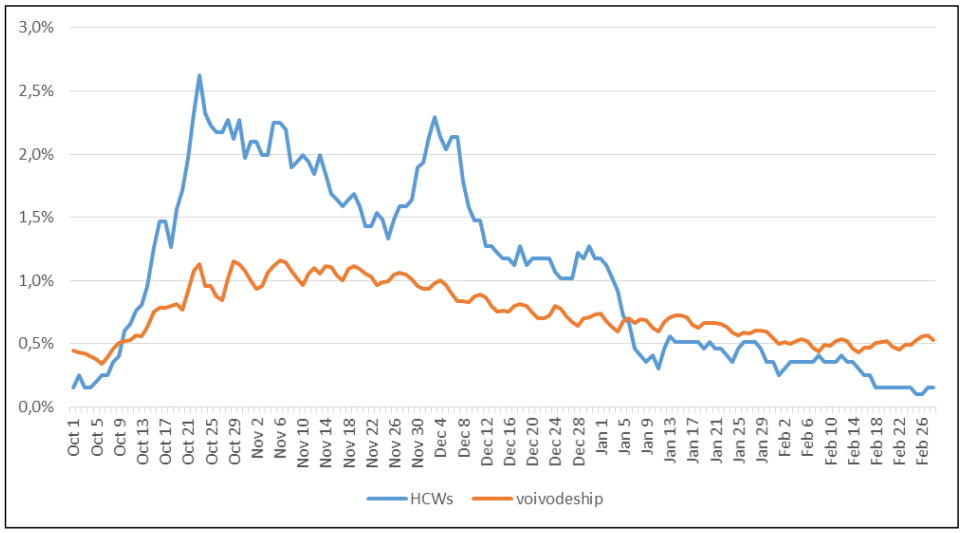


Figure 3. Daily quarantine rates in the healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz and the general population of the Kuyavian-Pomeranian Voivodeship

The differences between the general population of the Kuyavian-Pomeranian Voivodeship and the population of HCWs of Antoni Jurasz University Hospital No. 1. in Bydgoszcz regarding SARS-CoV-2 incidence rate were deemed statistically significant ($p = 0.00$). A comparison between those groups based on the percentage of the population with new confirmed SARS-CoV-2 cases per month is shown in Figure 2. Also, statistically significant differences were found between the rates of infection in every occupational group, including administrative and technical workers of the hospital, in comparison with the regional rates.

A comparison of daily quarantine rates (percentage of people on quarantine in accordance to a total number of people in an analysed group per day) between the general population of the Kuyavian-Pomeranian Voivodeship and HCWs in total is shown in Figure 3. Statistically significant differences ($p = 0.00$) were found (Fig. 4). Additionally, the occupational groups of HCWs were compared. Statistically significant differences were found between almost all the analysed HCWs groups. Daily quarantine rates were not found to be statistically different only in the case of the comparison between doctors and other medical staff members.

The number of man-days lost due to quarantines of HCWs has been calculated for each HCWs group for each month as shown in Table 1. November was the most affected month with 1047 man-days lost solely to quarantines and with the highest rates of man-days lost in almost all of the groups. Only the rates in doctors were the highest in a different month, in December.

The absenteeism of HCWs during the COVID-19 pandemic was also assessed by the number of hospital employees on sick leave between October and February 2020/2021 in comparison to the corresponding period from a year before (2019/2020) as shown in Figure 5. Statistically significant differences ($p = 0.00$) were found between the 2019/2020 and 2020/2021 periods (Fig. 6).

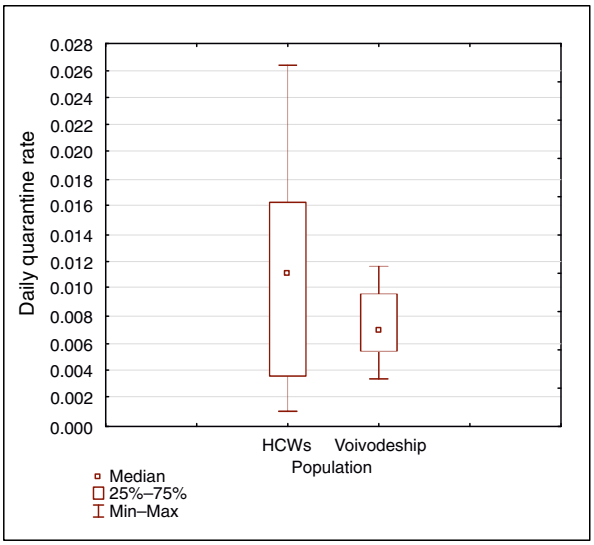


Figure 4. A comparison of daily quarantine rates in the healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz and the general population of the Kuyavian-Pomeranian Voivodeship

Discussion

The presented analysis constitutes one of the few currently available attempts to assess the incidence of COVID-19 in health care workers and their absenteeism regarding the stability of the workforce in a hospital setting. The use of sick leave data and the calculation of lost man-days as a measuring method was found to be a novel approach to this topic, as well as analysing the impact of COVID-19 on healthcare workers not only in the context of the hospital population itself but also in a comparison with the regional trends.

The analysed period is in keeping with an outburst of the second wave of COVID-19 in Poland, therefore a pronounced peak in the number of SARS-CoV-2 infections can be seen in the presented analysis between October and December of 2020.

Several studies have been conducted so far to evaluate the impact of COVID-19 on HCWs in general and in specific groups within that population. In a study by Rudberg et al. [5] the seroprevalence of SARS-CoV-2 IgG antibodies was found to be 19.1% among 2149 HCWs of a hospital in Sweden, which constitutes a higher rate than the regional values determined for the same period. Additionally, a nationwide linkage cohort study led by Shah et al. [6] in Scotland, UK, indicated that the risk of hospital admission for COVID-19 was similar in non-patient-facing HCWs and the general population. However, a comparison of patient-facing and non-patient-facing HCWs showed that the former is at a greater risk than the latter, with the highest risk in specific occupational groups such as paramedics and medical personnel working in acute receiving specialities.

Another study that aimed to assess occupational risks of SARS-CoV-2 infection in HCWs was a prospective observational study conducted by Eyre et al. [7] at Oxford University Hospitals, UK. The highest infection rates were found in porters and cleaners (18.6%), while the lowest in administrative staff (7.2%). Contrastingly,

Table 1. Monthly rates of man-days lost due to quarantines of HCWs divided into occupational groups

HCWs group	October	November	December	January	February
Doctors	139 / 10664 (1.30%)	78 / 9390 (0.83%)	201 / 10075 (**2.00%**)	45 / 10106 (0.45%)	8 / 9408 (0.09%)
Nurses	274 / 22599 (1.21%)	494 / 21930 (**2.25%**)	428 / 22506 (1.90%)	157 / 22475 (0.70%)	102 / 20412 (0.50%)
Administrative and technical workers	82 / 8742 (0.94%)	113 / 8460 (**1.34%**)	11 / 8804 (0.12%)	71 / 8680 (0.82%)	14 / 7868 (0.18%)
Other medical staff members	280 / 19344 (1.45%)	362 / 18870 (**1.92%**)	232 / 19468 (1.19%)	59 / 19375 (0.30%)	20 / 17472 (0.11%)
HCWs in total	775 / 61349 (1.26%)	1047 / 58650 (**1.79%**)	872 / 60853 (1.43%)	332 / 60636 (0.55%)	144 / 55160 (0.26%)

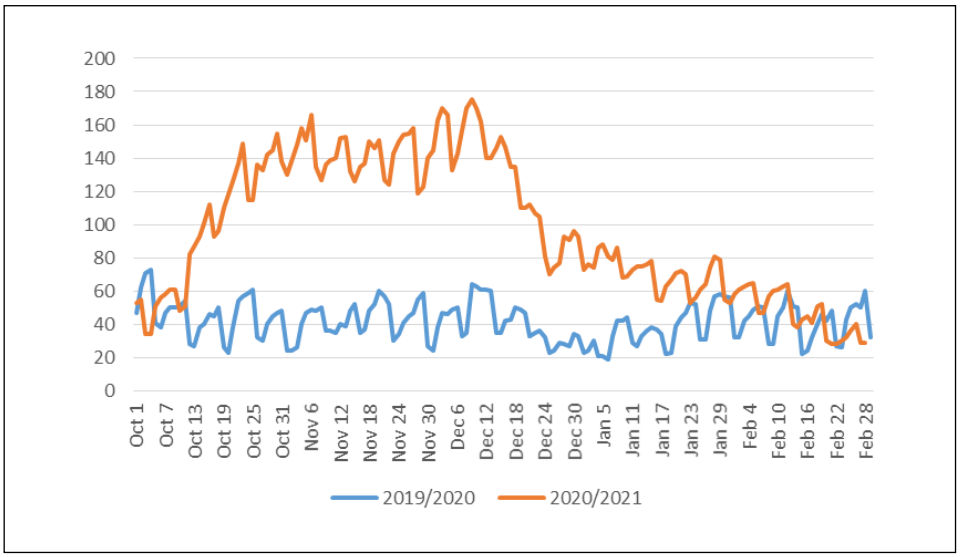


Figure 5. Daily number of healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz on sick leave between the 1st of October and the 28th/29th of February in years 2019/2020 and 2020/2021

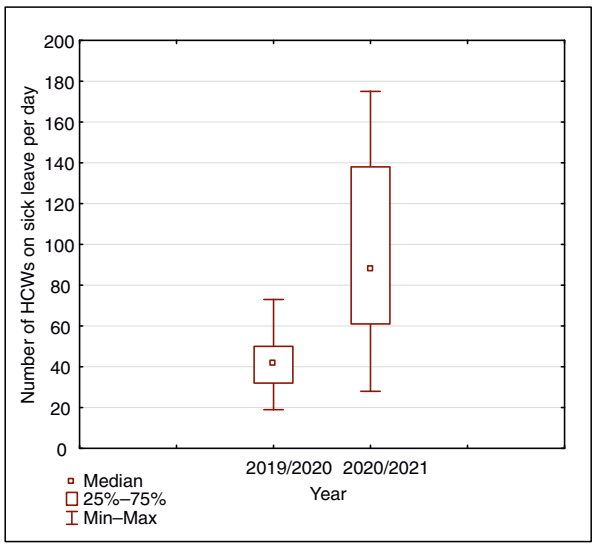


Figure 6. A comparison of the daily number of healthcare workers of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz on sick leave from the 1st of October to the 28th/29th of February 2019/2020 and 2020/2021

a study by Garzaro et al. [8] from a university hospital in Italy determined a statistically increased risk of being infected among HCWs only in physicians and administrative staff as well as in non-medical services. However, an analysis conducted by Kantele et al. [9] at Helsinki University Hospital, Finland, did not find significant differences between HCWs groups (physicians, nurses, etc.) regarding COVID-19 incidence but rather an association with their working area (non-ICU vs. ICU). While most studies do indicate a higher risk of SARS-CoV-2 infections among HCWs, the results regarding specific occupational groups are not consistent. The differences between the available analyses as well as the one that we have conducted might suggest varying levels of staff training and the availability of protective equipment in specific healthcare facilities. In addition, the information about whether hospitals provide COVID-19 dedicated services (e.g., COVID-19 dedicated departments) should also be taken into account.

A much-needed attempt to analyse the impact of COVID-19 on HCWs in a global context was made by Bandyopadhyay et al. [10] in a form of a systematic review of infections and mortality worldwide through searches of bibliographic databases. The analysis report of 152,888 cases of infections and 1,413 cases of death with infections occurring mainly in nurses and deaths occurring mainly in doctors.

To maintain well-functioning healthcare systems around the world one needs to consider what are the most effective ways to protect HCWs. A questionnaire-based study of 103 HCWs diagnosed with COVID-19 has been conducted by Jin et al. [11] in a Wuhan hospital to assess perceived routes of infection. In 84.5% of the cases, the infection was assumed to occur in the hospital. A lack of proper training and equipment to protect against the virus are factors often regarded as causative to a high percentage of infections among HCWs [12]. The urgent need for improvements in HCWs' security and the restructuration of healthcare systems worldwide was also raised by Pruc et al. [12]. Moreover, the authors underlined the current lack of pre-

cise data on the incidence of COVID-19 in HCWs. This proves the importance of the analysis we have conducted. Still, further research in this area is needed.

The limitations of this study pertain to the fact that HCWs might have had a higher rate of SARS-CoV-2 testing than the general population, e.g., due to different testing policies or higher awareness of health-related issues among HCWs. This might have caused a higher detectability of the infections and therefore higher rates of infections among this group.

Conclusions

Healthcare workers are a group significantly affected by the COVID-19 pandemic, which can be observed through higher rates of infections and quarantines, especially in nurses and doctors.

The COVID-19 pandemic has influenced the stability and availability of the workforce in the hospital both directly (infections, quarantines) and indirectly (sick leave).

Further studies in the area of HCWs' security are needed.

Statement of competing interests: *Jacek Kryś is an employee of the Antoni Jurasz University Hospital No. 1. in Bydgoszcz.*

List of abbreviations:

COVID-19 — coronavirus disease 2019
HCWs — healthcare workers
SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2

References

1. Serwis Rzeczypospolitej Polskiej. Ministerstwo Zdrowia. Pierwszy przypadek koronawirusa w Polsce. https://www gov pl/web/zdrowie/pierwszy-przypadek-koronawirusa. (16.03.2021).
2. Serwis Rzeczypospolitej Polskiej. Wojewódzka Stacja Sanitarno-Epidemiologiczna w Bydgoszczy. Dane epidemiologiczne dotyczące zachorowań na COVID-19 w województwie kujawsko-pomorskim. https://www gov pl/web/wsse-bydgoszcz/dane-epidemiologiczne-dotyczace-zachorowan-na-covid-19-w-wojewodztwie. (16.03.2021).
3. Serwis Rzeczypospolitej Polskiej. Raport zakażeń koronawirusem (SARS-CoV-2). https://www gov pl/web/koronawirus/wykaz-zarazen-koronawirusem-sars-cov-2. (16.03.2021).
4. Główny Urząd Statystyczny. Ludność. Stan i struktura ludności oraz ruch naturalny w przekroju terytorialnym (stan w dniu 30. https://stat gov pl/obszary-tematyczne/ludnosc/ludnosc-stan-i-struktura-ludnosci-oraz-ruch-naturalny-w-przekroju-terytorialnym-stan-w-dniu-30-06-2020,6,28 html. (16.03.2021).
5. Rudberg AS, Havervall S, Månberg A, et al. SARS-CoV-2 exposure, symptoms and seroprevalence in healthcare workers in Sweden. Nat Commun. 2020; 11(1): 5064, doi: 10.1038/s41467-020-18848-0, indexed in Pubmed: 33033249.
6. Shah ASV, Wood R, Gribben C, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study. BMJ. 2020; 371: m3582, doi: 10.1136/bmj.m3582, indexed in Pubmed: 33115726.
7. Eyre DW, Lumley SF, O'Donnell D, et al. Oxford University Hospitals Staff Testing Group. Differential occupational risks to healthcare workers from SARS-CoV-2 observed during a prospective observational study. Elife. 2020; 9, doi: 10.7554/eLife.60675, indexed in Pubmed: 32820721.
8. Garzaro G, Clari M, Ciocan C, et al. COVID-19 Infection and Diffusion Among the Healthcare Workforce in a Large University-Hospital in Northwest Italy. SSRN Electronic Journal. , doi: 10.2139/ssrn.3578806.
9. Kantele A, Lääveri T, Kareinen L, et al. SARS-CoV-2 infections among healthcare workers at Helsinki University Hospital, Finland, spring 2020: Serosurvey, symptoms and risk factors. Travel Med Infect Dis. 2021; 39: 101949, doi: 10.1016/j.tmaid.2020.101949, indexed in Pubmed: 33321195.
10. Bandyopadhyay S, Baticulon RE, Kadhum M, et al. Infection and mortality of healthcare workers worldwide from COVID-19: a systematic review. BMJ Glob Health. 2020; 5(12), doi: 10.1136/bmjgh-2020-003097, indexed in Pubmed: 33277297.
11. Jin YH, Huang Q, Wang YY, et al. Perceived infection transmission routes, infection control practices, psychosocial changes, and management of COVID-19 infected healthcare workers in a tertiary acute care hospital in Wuhan: a cross-sectional survey. Mil Med Res. 2020; 7(1): 24, doi: 10.1186/s40779-020-00254-8, indexed in Pubmed: 32393381.
12. Pruc M, Golik D, Szarpak L, et al. COVID-19 in healthcare workers. Am J Emerg Med. 2021; 39: 236, doi: 10.1016/j.ajem.2020.05.017, indexed in Pubmed: 32414525.

VIA MEDICA

REVIEW ARTICLE

Przemysław Musz[1], Przemysław Podhajski[2], Klaudyna Grzelakowska[3], Julia M. Umińska[4]

[1]IMER systems, Wroclaw, Poland
[2]Department of Cardiology and Internal Medicine, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland
[3]Faculty of Medicine, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland
[4]Department of Geriatrics, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland

Non-invasive assessment of endothelial function — a review of available methods

Corresponding author:

Julia M. Umińska, Department of Geriatrics, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland, e-mail: julia.uminska@cm.umk.pl

Medical Research Journal 2021; Volume 6, Number 1, 53–58
10.5603/MRJ.a2021.0008

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

The key role of the endothelium in vascular-dependent diseases led to an increase in scientific interest in examining the endothelial function as a tool for screening, as well as for monitoring of the disease and its treatment. In the period from 2016 till 2019, a high level of scientific interest in the assessment of endothelial function has been observed, as expressed in the number of published clinical trials between 369 and 477 per year with the total number of subjects between 49,634 and 75,934.

Currently, none of the known methods of assessing vascular endothelial function is widely used in clinical practice. This may be a result of various factors: scientific (lack of standardization in terms of quantitative indicators of endothelial function), formal (lack of official recommendations for endothelial assessment), financial (the best-validated methods and devices are costly, which renders it unsustainable to use them in screening diagnostics) and technological (high susceptibility of many measurement methods to errors). Nevertheless, it can be expected that non-invasive methods for the early detection of endothelial dysfunction in screening programs will gradually gain importance.

Key words: endothelium, endothelial function, endothelial assessment

Med Res J 2021; 6 (1): 53–58

Introduction

Endothelial dysfunction precedes the appearance of atherosclerotic lesions and their clinical symptoms. Early pathology detection allows the implementation of adequate preventive treatment [1–6]. The study aimed to review non-invasive methods of endothelial function assessment as an attractive option for early diagnosis and an interesting research area.

Endothelial function assessment — general assumptions

The vast majority of non-invasive methods for endothelial function assessment are based on the phenomenon of reactive hyperaemia. The flow-mediated dilation (FMD) method is based on the ability of endothelium cells to regulate peripheral resistance, while endothelial dysfunction is defined as the impairment of vasodilation due to the secretion of endothelium-derived relaxing factor EDRF [7–10]. The identification of EDRF as nitric oxide (NO) was awarded the Nobel Prize in 1998 [11, 12].

Among the factors modulating the vascular endothelium function, shear stress is the most convenient to apply in clinical practice. The sudden change of shear stress leads to the reactive hyperaemia commonly used in non-invasive tests of the endothelium. The post-occlusion reactive hyperaemia (PORH) is defined as an increase in blood flow following the artery occlusion due to EDRF release [13, 14]. While not all details of the mechanism of reactive hyperaemia have been established so far, a general pattern can be drawn in the form of a cause-and-effect sequence following the artery occlusion (i.e., deflation of the occlusive cuff). The decrease in peripheral resistance due to vasodilation of the arterioles causes an analogous blood flow increase in the conduit arteries. An increase in blood flow causes a proportional increase in shear forces, and this directly induces endothelial cell mechanoreception pathways resulting in the increased secretion of nitric oxide, which, in turn, causes vasodilation of the conduit arteries [15, 16].

Application of endothelial function assessment in clinical studies

The key role of the endothelium in vascular-dependent diseases has led to an increase in scientific interest in examining the endothelial function as a tool for screening, as well as for monitoring of the disease and its treatment [13–16]. Apart from the already existing atherosclerosis, the functioning of the vascular endothelium is influenced by, among others:

— Arterial hypertension,
— Hyperlipidaemia,
— Diabetes mellitus,
— Hyperhomocysteinaemia,
— Heart failure,
— Tobacco smoking,
— Age,
— Inflammatory factors,
— Menopause [1, 2, 17].

Recently, a considerable number of studies applying endothelial function assessment as a research tool have been published. The authors conducted a search covering the period from 1st January 2016 to 31st December 2020 using the MEDLINE database with "endothelial function" as the only keyword. The initial search revealed 61,399 records. Only 1,873 of those articles, classified as clinical trials, were included for further analysis. References of those studies were searched manually for studies in which endothelial function was assessed. The final analysis comprised 1,742 studies in which several subjects who underwent endothelial function assessment was reported. For each eligible study, the number of studied subjects was defined (Tab. 1).

In the period from 2016 till 2019, a high level of scientific interest in the assessment of endothelial function has been observed, as expressed in the number of published clinical trials between 369 and 477 per year with the total number of subjects between 49,634 and 75,934. The sudden decline in the number of published studies and the total number of participants seen in 2020 is likely an effect of the COVID-19 pandemic. Therefore, a further increase in the number of such studies should be assumed once the restrictions are eased. It should be emphasized that the performed analysis was limited using only one keyword in one of the most prestigious databases, which groups only the best scientific journals and the yet impressive total number of 262,218 people who underwent assessment of endothelial function was reported. Thus, the actual number of endothelial function tests carried out in the analysed period might have been much higher.

Methods of endothelial function assessment

Understanding the importance, and thus the growing interest in endothelial pathophysiology has led to the development of several methods for invasive or non-invasive, quantitative evaluation of its function [1–4]. Most of these methods are based on the assumptions: that firstly certain types of stimulation trigger the nitric oxide production leading to local vasodilation, and secondly endothelial dysfunction is a systemic disorder, therefore can be tested in any arterial vessels, most often on easily accessible arteries of the upper limbs [18]. To determine the severity of the endothelial reaction the baseline (reference level) of the assessed parameter should be defined as a reference to its value after the stimulation. Some methods need to employ additional mathematical methods to compensate for the effects of extra-endothelial factors that may interfere with the measurement of the local response [19].

In-vitro methods

The in-vitro methods of endothelial function assessment are based on the analysis of the concentration of the vasoactive factor in the plasma. Direct measurement of NO concentration is not feasible in everyday clinical practice, and the available techniques are burdened with a considerable error. However, it is possible to assess the concentration of other substances functionally related to the endothelium [1, 2, 17]. The most commonly used markers of endothelial function include:

Table 1. Trials applying endothelial function assessment

Year	Number of clinical trials	Number of clinical trials reporting of number of participants	Number of participants
2016	477	434	75,934
2017	432	399	54,673
2018	369	352	50,095
2019	400	374	49,634
2020	195	183	31,882
Total:	1,873	1,742	262,218

— Von Willebrand factor,
— Thrombomodulin,
— Intercellular adhesive molecule (ICAM-1),
— Vascular adhesive molecule (VCAM-1),
— Plasminogen inhibitor type 1 (PAI-1),
— P-selectin and E-selectin,
— Vascular endothelial growth factor (VEGF) [1, 2, 10, 17].

Another in-vitro test showing damage to the vascular endothelium may be a measurement of the number of circulating endothelial cells (CEC) in the blood. The increase of CEC correlates with other endothelial markers, including von Willebrand factor, E-selectin and thrombomodulin [1,2,4-6,10].

Invasive in-vivo methods

Invasive methods of endothelial function assessment are mainly used in scientific research due to the significant risk of complications resulting from the specificity of endovascular procedures [9, 14]. The use of invasive techniques was necessary to establish a reference standard for the validation of completely safe non-invasive methods. Assessment of coronary response to local acetylcholine injection introduced in the 1990s is a widely accepted method. Vasoconstriction caused by endothelial dysfunction is recorded indirectly by measuring the coronary flow with an endovascular Doppler probe or with thermodilution. The measure of the coronary arteries lumen with quantitative angiography is an alternative to the coronary flow assessment [20]. A positron emission tomography (PET) scanner [22] and magnetic resonance imaging (MRI) with phase contrast [21] were also used to quantify the hyperaemic response to the administration of vasoactive agents.

Non-invasive in-vivo methods

Flow-mediated skin fluorescence (FMSF)

One of the non-invasive methods of endothelial function assessment is the measurement of fluorescence [23]. The FMSF is based on the fluorescence measurement of the reduced form of nicotinamide adenine dinucleotide (NADH), emitted by the skin cells in the band of 420 to 480 nm (peak emission in the range 455–465 nm) in response to excitation by UV light in the 300 to 400 nm range (recommended range is 345–355 nm). The test consists of three phases: recording the baseline intensity of the fluorescence (usually 1–2 minutes); occlusion phase (usually 5 minutes); registration of the response (decay of the NADH fluorescence intensity to the baseline, time — up to 15 minutes) [23]. FMSF allows determining the tissues and vascular bed response during ischaemia, while the classic techniques based on FMD are based on a vasomotor reactivity examination [24].

FMD-based methods

The phenomenon of reactive hyperaemia is the methodological foundation for almost all currently used non-invasive techniques for endothelial function assessment. This group of methods is derived from the classic technique based on the use of ultrasound for direct visualization of brachial artery dilation, which is associated with operator-dependent bias. Therefore, intensive research is conducted on the development of semi-automatic or fully automatic techniques, i.e., techniques that do not require the active participation of the operator during the test.

Classic FMD method

The classic FMD method assessing the intensity of reactive hyperaemia consists of three phases: measurement of the diameter of a selected artery (e.g., brachial); stimulation phase; measurement after stimulation. As a stimulation, transient ischaemia caused by tightening the sphygmomanometric cuff (by inflating it to pressure 30 to 50 mmHg higher than the baseline systolic blood pressure), is usually applied [9–12,16, 22, 25]. Only a few publications have reported the use of intra-arterial injection of a vasoactive agent: nitro-glycerine [16], acetylcholine or methacholine [9–11, 26]. The relative change in vessel diameter is rather small, assuming values ranging from a few to several per cent compared to the pre-occlusion measurement [14, 16, 25].

Reactive hyperaemia peripheral arterial tonometry (RH-PAT)

RH-PAT — a modified FMD method is used in the EndoPAT device (Itamar Medical Ltd.) [27–30]. This method uses finger probes with a two-compartment pneumatic cuff. The proximal cuff is pumped up to a pressure close to the diastolic blood pressure of the patient, and its task is to relieve the arteries walls and reduce the volume of venous blood in the area of the second phalanx of the examined finger [27]. The distal cuff, separately connected to the measurement system, is used for the actual measurement by pneumatic plethysmography. The method has been extensively validated in many publications as a diagnostic and predictive tool in terms of vascular risk assessment [27–32].

Thermal method

The thermal method used in VENDYS devices (Endothelix Inc.) is based on recording the temperature of two fingers (e.g., index fingers), with one used as a reference, and the other stimulated with a classic 5-minute occlusion with an automatically pumped cuff [33]. The tightening of the cuff causes a decrease in the occluded limb's skin temperature in comparison to the baseline temperature recorded before cuff inflation. Based on the rate of the temperature decay and with the use of

a mathematical model, a zero-reactivity curve (ZRC) is determined. The third segment of the temperature curve recorded after the restoration of perfusion refers to the ZRC line and normalized to the reference record from the unoccluded (reference) limb. Based on the record from the third phase of measurement, a curve of the hyperaemic response is drawn [33]. The peak temperature, defined as the maximum point of this curve, represents the Vascular Reactivity Index (VRI) [33, 34].

Enclosed-zone FMD (EZ-FMD) method

This method is based on the oscillometric blood pressure measurement, where the cuff inflation and deflation cycle is repeated six times: at the beginning of the measurement (once) to determine the patient's maximum pulse amplitude and five times after a 5-minute of a total occlusion. The EZ-FMD coefficient is calculated from the formula based on the maximum systolic peak in the pre-occlusion phase and the highest peak in the post-occlusion phase [35, 36].

Photoplethysmography method — reactive hyperemia peripheral arterial volume (RH-PAV)

Classic pulse oximetry sensors in the form of finger clips can also be used to test endothelial function. A LED diode operating in the near-infrared region (940 nm) is used for the test. The methodology of calculating the result is analogous to that of the RH-PAT index: the average amplitudes are calculated from two signal intervals recorded: 40 s before occlusion and 40 s after cuff deflation. The results are normalized to the opposite non-occluded limb. The authors of the described technique called it RH-PAV [37].

Impedance plethysmography method

Impedance plethysmography uses changes in the electrical impedance of tissues caused by pulsatile blood flow. For reactive hyperaemia studies, local injection of acetylcholine or methacholine directly into one of the forearm arteries was used [21].

Laser speckle contrast imaging (LSCI) method

LSCI is based on the analysis of speckle pattern images, formed when illuminating the patient's skin surface with laser light. LSCI allows for two-dimensional visualization of peripheral perfusion in the form of a colour map. This method was used to acquire images of perfusion changes occurring under the influence of acetylcholine and in response to classical stimulation with temporary artery occlusion [38, 39].

Laser Doppler flowmetry (LDF) method

LDF is used to assess peripheral microcirculation, including the measurement of reactive hyperaemia. With regard to vascular endothelial studies, the LDF method is used to assess reactive hyperaemia in the vascular bed of cutaneous vessels. Laser flow meters are well suited for recording the early component of the hyperaemic response associated with rapid dilation of resistance-type vessels (skin arterioles) [41, 42].

Pulse velocity wave (PVW) measurement method

This method is based on the measurement of the delay of the peak of the peripheral pulse wave, usually in relation to the QRS complex in a simultaneously recorded ECG — the greater the stiffness of the vessels, the faster the pulse wave propagation is observed [43].

The delay is calculated from measurements taken at two different points of the body, such as the carotid and femoral arteries. This technique can also be used for endothelial studies [44]. Depending on the adopted pulse wave recording points, it is possible not only to study the central arterial stiffness but also the peripheral regardless of the condition of the aorta. The stiffness of the arterial wall depends on the vessel ultrastructure, blood pressure and tone of the vascular muscle layer, all varying with age. The use of pulse wave velocity measurement in endothelial studies is based on the assumption that the administration of vasodilators to the patient allows the extraction of the last of these components. Available studies showed a negative correlation between PWV values and endothelial function [43, 44].

Pulse wave analysis (PWA) method

PWA is based on the mathematical decomposition of the pulse waveform recorded on the peripheral (usually radial) artery. Based on the relation of the timing and the amplitude data several parameters reflecting different aspects of central haemodynamics are determined. Similarly to the PWV technique, the pulse wave analysis may also be supported by pharmacological stimulation to determine the range of vascular endothelium response to the administration of vasoactive agents [44, 45].

Summary

Endothelial dysfunction playing a pivotal role in the pathophysiology of several civilization diseases can be detected at the asymptomatic stage. Therefore, a non-invasive assessment of endothelial function can be applied for early screening in people at increased cardiovascular risk. Moreover, endothelial function assessment can be used as a method for evaluation of treatment effectiveness, as well as for adherence to treatment [46–57]. However, until now these methods have usually been used only for research purposes, and their potential clinical application should be preceded by clinical trials.

Recent studies indicate the endothelium as the main target of SARS-CoV-2, which often causes thrombotic complications [58–60]. Therefore, studies aimed to assess the usefulness of testing the endothelial function also seem advisable in patients with COVID 19.

Currently, none of the known methods of assessing vascular endothelial function is widely used in clinical practice. This may be a result of various factors: scientific (lack of standardization in terms of quantitative indicators of endothelial function), formal (lack of official recommendations for endothelial assessment), financial (the best-validated methods and devices are costly, which renders it unsustainable to use them in screening diagnostics) and technological (high susceptibility of many measurement methods to errors).

Nevertheless, it can be expected that non-invasive methods for the early detection of endothelial dysfunction in screening programs will gradually gain importance.

References

1. Obońska K, Grąbczewska Z, Fisz J. Ocena czynności śródbłonka naczyniowego — gdzie jesteśmy, dokąd zmierzamy? Folia Cardiologica Excerpta. 2010; 5: 292–297.
2. Obońska K, Grąbczewska Z, Fisz J, et al. , Cukrzyca i dysfunkcja śródbłonka — krótkie spojrzenie na złożony problem, Folia Cardiologica Excerpta. 2011; 6: 109–116.
3. Koziński M, Kubica J. [Inflammatory response after coronary angioplasty — mechanisms and significance]. Kardiol Pol. 2006; 64(7): 771–4; author reply 775, indexed in Pubmed: 16886140.
4. Grabczewska Z, Kubica J. In search of understanding the endothelium. Cardiol J. 2008; 15(4): 229–232, indexed in Pubmed: 18698537.
5. Grabczewska Z, Thews M, Góralczyk K, et al. Endothelial function in patients with chest pain and normal coronary angiograms. Kardiol Pol. 2007; 65(10): 1199–206; discussion 1207, indexed in Pubmed: 17979048.
6. Lampka M, Grąbczewska Z, Jendryczka-Maćkiewicz E, et al. Circulating endothelial cells in coronary artery disease. Kardiol Pol. 2010; 68(10): 1100–1105, indexed in Pubmed: 20967702.
7. dela Paz NG, D'Amore PA. Arterial versus venous endothelial cells. Cell Tissue Res. 2009; 335(1): 5–16, doi: 10.1007/s00441-008-0706-5, indexed in Pubmed: 18972135.
8. Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol. 2007; 49(25): 2379–2393, doi: 10.1016/j.jacc.2007.02.059, indexed in Pubmed: 17599600.
9. Anderson T. Assessment and treatment of endothelial dysfunction in humans. Journal of the American College of Cardiology. 1999; 34(3): 631–638, doi: 10.1016/s0735-1097(99)00259-4.
10. Furchgott RF, Cherry PD, Zawadzki JV, et al. Endothelial Cells as Mediators of Vasodilation of Arteries. Journal of Cardiovascular Pharmacology. 1984; 6: S336–S343, doi: 10.1097/00005344-198406002-00008.
11. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980; 288(5789): 373–376, doi: 10.1038/288373a0, indexed in Pubmed: 6253831.
12. Furchgott R. Endothelium-Derived Relaxing Factor: Discovery, Early Studies, and Identification as Nitric Oxide. Bioscience Reports. 1999; 19(4): 235–251, doi: 10.1023/a:1020537506008.
13. Lorenzo S, Minson CT. Human cutaneous reactive hyperaemia: role of BKCa channels and sensory nerves. J Physiol. 2007; 585(Pt 1): 295–303, doi: 10.1113/jphysiol.2007.143867, indexed in Pubmed: 17901123.
14. Papaioannou TG, Stefanadis C. , Vascular Wall Shear Stress: Basic Principles and Methods, Hellenic J Cardiol. 2005; 46: 9–15.
15. Shahzad KA, Qin Z, Li Y. The roles of focal adhesion and cytoskeleton systems in fluid shear stress-induced endothelial cell response. Biocell . 2020; 44(2): 137–145, doi: 10.32604/biocell.2020.08500.
16. Inoue T, Matsuoka H, Higashi Y, et al. Flow-Mediated Vasodilation as a Diagnostic Modality for Vascular Failure. Hypertension Research. 2008; 31(12): 2105–2113, doi: 10.1291/hypres.31.2105.
17. Goch A, Goch JH. , Wybrane parametry funkcji śródbłonka u chorych na niepowikłane nadciśnienie tętnicze z czynnikami ryzyka miażdżycy oraz bez nich, Nadciśnienie Tętnicze. 2005; 9: 118–125.
18. Atzeni F, Sarzi-Puttini P, Sitia S, et al. From endothelial dysfunction to atherosclerosis. Autoimmun Rev. 2010; 9(12): 830–834, doi: 10.1016/j.autrev.2010.07.016, indexed in Pubmed: 20678595.
19. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation. 2005; 111(3): 363–368, doi: 10.1161/01.CIR.0000153339.27064.14, indexed in Pubmed: 15668353.
20. Teragawa H, Ueda K, Matsuda K, et al. Relationship between endothelial function in the coronary and brachial arteries. Clin Cardiol. 2005; 28(10): 460–466, doi: 10.1002/clc.4960281004, indexed in Pubmed: 16274093.
21. Hadi HAR, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag. 2005; 1(3): 183–198, indexed in Pubmed: 17319104.
22. Foody JM. , Preventive Cardiology: Insights Into the Prevention and Treatment of Cardiovascular Disease, Humana Press, New Jersey. ; 2006: 253–255.
23. Gębicki J, Marcinek A, Chłopicki S. Sposób określania parametrów do oceny funkcji śródbłonka naczyniowego. Opis patentowy nr PL226889.
24. Tarnawska M, Dorniak K, Kaszubowski M, et al. A pilot study with flow mediated skin fluorescence: A novel device to assess microvascular endothelial function in coronary artery disease. Cardiol J. 2018; 25(1): 120–127, doi: 10.5603/CJ.a2017.0096, indexed in Pubmed: 28840593.
25. Uehata A, Lieberman EH, Gerhard MD. et. al. , Noninvasive assessment of endothelium-dependent flow-mediated dilation of the brachial artery, Vascular Medicine. 1997; 2: 87–92.
26. Ganz P, Vita JA. Testing endothelial vasomotor function: nitric oxide, a multipotent molecule. Circulation. 2003; 108(17): 2049–2053, doi: 10.1161/01.CIR.0000089507.19675.F9, indexed in Pubmed: 14581383.
27. Celermajer DS. Reliable endothelial function testing: at our fingertips? Circulation. 2008; 117(19): 2428–2430, doi: 10.1161/CIRCULATIONAHA.108.775155, indexed in Pubmed: 18474821.
28. Goor DA. et. al, Diagnosing medical conditions by monitoring of peripheral arterial tone, opis patentowy nr WO. ; 00: 74551.
29. Schnall RP. , Probe partucularly useful for non-invasive detection of medical conditions, opis patentowy nr WO. ; 01: 03569.
30. Lavie P, Schanll RP, Sheffy J. , Method and apparatus for th non-invasive detection of particular sleep-state conditons by monitoring the peripheral vascular system, opis patentowy nr WO. ; 01: 64101.
31. Obońska K, Grąbczewska Z, Koziński M, et al. Assessment of endothelial function in relation to the presence of type 2 diabetes mellitus in patients with prior myocardial infarction: a pilot study using peripheral arterial tonometry, Folia Medica Copernicana. 2014; 2: 42–48.
32. Grabczewska Z, Adamowicz A, Oboñska K, et al. Neither Cyclosporine nor Tacrolimus Deteriorate Endothelial Function in Renal Transplant Recipients Assessed with Reactive Hyperaemia Index. Transplantation Journal. 2012; 94(10S): 892, doi: 10.1097/00007890-201211271-01758.
33. Naghavi M, Yen AA, Lin AW. H., Tanaka H., Kleis S. , New Indices of Endothelial Function Measured byDigital Thermal Monitoring of Vascular Reactivity: Data from 6084 Patients Registry; International Journal of Vascular Medicine, 2016, Art. : ID.
34. Naghavi M, Yen A, Panthagani D, et al. Methods and apparatus for assessing vascular health, opis patentowy nr WO2015147796A1.
35. Hirano H, Takama R, Matsumoto R, et al. Assessment of Lower-limb Vascular Endothelial Function Based on Enclosed Zone Flow-mediated Dilation. Sci Rep. 2018; 8(1): 9263, doi: 10.1038/s41598-018-27392-3, indexed in Pubmed: 29915185.
36. Idei N, Ukawa T, Kajikawa M, et al. A novel noninvasive and simple method for assessment of endothelial function: enclosed zone flow-mediated vasodilation (ezFMD) using an oscillation amplitude measurement. Atherosclerosis. 2013; 229(2): 324–330, doi: 10.1016/j.atherosclerosis.2013.05.016, indexed in Pubmed: 23880183.
37. Si D, Ni L, Wang Y, et al. A new method for the assessment of endothelial function with peripheral arterial volume. BMC Cardiovasc Disord. 2018; 18(1): 81, doi: 10.1186/s12872-018-0821-5, indexed in Pubmed: 29728052.
38. Hellmann M, Dudziak M. , Analiza kontrastu obrazu spekli laserowych — nowa metoda oceny mikrokrążenia, Choroby Serca i Naczyń. 2013; 10: 91–94.

39. Cordovil I, Huguenin G, Rosa G, et al. Evaluation of systemic microvascular endothelial function using laser speckle contrast imaging. Microvasc Res. 2012; 83(3): 376–379, doi: 10.1016/j.mvr.2012.01.004, indexed in Pubmed: 22326551.
40. Tamura T. Blood Flow Measurement. Comprehensive Biomedical Physics. 2014: 91–105, doi: 10.1016/b978-0-444-53632-7.00511-6.
41. Maga P, Henry BM, Kmiotek EK, et al. Postocclusive Hyperemia Measured with Laser Doppler Flowmetry and Transcutaneous Oxygen Tension in the Diagnosis of Primary Raynaud's Phenomenon: A Prospective, Controlled Study. Biomed Res Int. 2016; 2016: 9645705, doi: 10.1155/2016/9645705, indexed in Pubmed: 28101516.
42. Schlager O, Hammer A, Willfort-Ehringer A, et al. Microvascular autoregulation in children and adolescents with type 1 diabetes mellitus. Diabetologia. 2012; 55(6): 1633–1640, doi: 10.1007/s00125-012-2502-8, indexed in Pubmed: 22366881.
43. Gurovich AN, Braith RW. Pulse wave analysis and pulse wave velocity techniques: are they ready for the clinic? Hypertens Res. 2011; 34(2): 166–169, doi: 10.1038/hr.2010.217, indexed in Pubmed: 21107336.
44. McEniery CM, Wallace S, Mackenzie IS, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. Hypertension. 2006; 48(4): 602–608, doi: 10.1161/01.HYP0000239206.64270.5f, indexed in Pubmed: 16940223.
45. Idei N, Ukawa T, Kajikawa M, et al. A novel noninvasive and simple method for assessment of endothelial function: enclosed zone flow-mediated vasodilation (ezFMD) using an oscillation amplitude measurement. Atherosclerosis. 2013; 229(2): 324–330, doi: 10.1016/j.atherosclerosis.2013.05.016, indexed in Pubmed: 23880183.
46. Grześk G, Kozinski M, Tantry US, et al. High-dose, but not low-dose, aspirin impairs anticontractile effect of ticagrelor following ADP stimulation in rat tail artery smooth muscle cells. Biomed Res Int. 2013; 2013: 928271, doi: 10.1155/2013/928271, indexed in Pubmed: 23841099.
47. Grzesk G, Kozinski M, Navarese EP, et al. Ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced vascular smooth muscle cell contraction: a placebo-controlled study in rats. Thromb Res. 2012; 130(1): 65–69, doi: 10.1016/j.thromres.2011.12.029, indexed in Pubmed: 22265722.
48. Koziński M, Sukiennik A, Sinkiewicz W, et al. [Drug-eluting stent-associated thrombosis: clinical relevance of impaired vessel-wall healing]. Postepy Hig Med Dosw (Online). 2008; 62: 185–205, indexed in Pubmed: 18464681.
49. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. Patient Prefer Adherence. 2018; 12: 333–340, doi: 10.2147/PPA.S150435, indexed in Pubmed: 29551891.
50. Kubica A, Kosobucka A, Fabiszak T, et al. Assessment of adherence to medication in patients after myocardial infarction treated with percutaneous coronary intervention. Is there a place for newself-reported questionnaires? Curr Med Res Opin. 2019; 35(2): 341–349, doi: 10.1080/03007995.2018.1510385, indexed in Pubmed: 30091642.
51. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. Curr Med Res Opin. 2016; 32(8): 1441–1451, doi: 10.1080/03007995.2016.1182901, indexed in Pubmed: 27112628.
52. Kubica A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol. 2014; 742: 47–54, doi: 10.1016/j.ejphar.2014.08.009, indexed in Pubmed: 25199965.
53. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. Sci Rep. 2020; 10(1): 12028, doi: 10.1038/s41598-020-68915-1, indexed in Pubmed: 32694522.
54. Kubica A, Obońska K, Kasprzak M, et al. Prediction of high risk of non-adherence to antiplatelet treatment. Kardiol Pol. 2016; 74(1): 61–67, doi: 10.5603/KP.a2015.0117, indexed in Pubmed: 26101025.
55. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. Pharmacology. 2015; 95(1-2): 50–58, doi: 10.1159/000371392, indexed in Pubmed: 25592409.
56. Kubica A, Kosobucka A, Michalski P, et al. Self-reported questionnaires for assessment adherence to treatment in patients with cardiovascular diseases. Medical Research Journal. 2018; 2(4): 115–122, doi: 10.5603/mrj.2017.0015.
57. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0005, indexed in Pubmed: 32037501.
58. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020; 116(10): 1666–1687, doi: 10.1093/cvr/cvaa106, indexed in Pubmed: 32352535.
59. Pons S, Fodil S, Azoulay E, et al. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care. 2020; 24(1): 353, doi: 10.1186/s13054-020-03062-7, indexed in Pubmed: 32546188.
60. Navarese EP, Musci RL, Frediani L, et al. Ion channel inhibition against COVID-19: A novel target for clinical investigation. Cardiol J. 2020; 27(4): 421–424, doi: 10.5603/CJ.a2020.0090, indexed in Pubmed: 32643141.

VIA MEDICA

REVIEW ARTICLE

Isaac I. Olufadewa[1,2,3], Miracle A. Adesina[1,2,4], Funmilayo R. Abudu[1,5], Samuel D. Ayelawa[1,5], Ruth I. Oladele[1,2], Yusuf Babatunde[1,6], Moyinoluwa J. Oladoye[1,7], Oluwadara T. Akano[1,5]

[1]Slum and Rural Health Initiative Research Academy, Ibadan, Nigeria
[2]College of Medicine, University of Ibadan, Ibadan, Nigeria
[3]Pan African University of Life and Earth Sciences Institute
[4]Universal Care for Africa Foundation, St. Louis, United States
[5]College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria
[6]Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria
[7]Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria

The role of comprehensive sexuality education (CSE) in reimagining HIV/AIDS inequalities

Corresponding author:
Ruth Oladele, Slum and Rural Health Initiative Research Academy, Ibadan, Nigeria, e-mail: roladele20@gmail.com

Medical Research Journal 2021; Volume 6, Number 1, 59–63
10.5603/MRJ.a2021.0006

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Over 70 million people globally have been infected with HIV since the beginning of the epidemic. HIV infection has neither a cure nor a vaccine; hence, education and awareness have been adopted to prevent the spread of the virus. Despite the action to reduce the HIV prevalence with access to effective information, prevention, diagnosis, treatment, and care, it remains a major health concern and a chronic health condition that could only be managed by enabling people living with the condition a better, longer, and healthy life. However, comprehensive sexuality education (CSE), which is a right-based approach that provides and equips people with the right knowledge on sexual education and reproductive health, can be utilised in sexual health promotion. It comprises seven essential components that focus on several aspects of sexuality. Thus, this paper provides evidence for the importance of CSE in reducing HIV prevalence, especially amongst the vulnerable population. The incorporation of long-term sexuality education programs in the school-based curriculum will contribute to the massive reduction in teenage pregnancies and abortion, and the decline in rates of sexually transmitted infections and HIV. It will also increase the knowledge about sexual and reproductive issues normalization and self-efficacy. Hence, CSE health educators and school teachers should be adequately trained in comprehensive sexuality education to curb the spread of HIV infection.

Key words: comprehensive sexuality education; cSE; gender inequality; HIV inequality

Med Res J 2021; 6 (1): 59–63

Introduction

Comprehensive sexuality education (CSE) according to the Sexuality Information and Education Council of the United States (SIECUS), is defined as a life-long process of acquiring information and forming attitudes, beliefs, and values about identity, relationships, and intimacy [1]. It involves all kinds of right-based approach to pass and equip people with sexual education, including knowledge on reproductive health, Human Immunodeficiency Virus (HIV), family planning, disease prevention, embryology and anatomy, skills and attitude needed for the individual sexuality to be enjoyable [2, 3]. CSE centres on gender and human rights-based approach which could also be regarded as family life education, sex education, life skills education, or sometimes holistic sexuality education depending on the setting where the program is done [2]. CSE is not about getting information alone but allowing young people to explore and build the right attitudes toward their sexuality which will later be a great gain for them in the future [3, 4]. Different climes start their sexuality education at a different age. In some parts of Western Europe, the most common age is between 4–5 years onward while most countries start at age 12–14 years onward [5].

Following the estimate of 38 million people living with HIV as of September 2018, it shows that 8 million people are not aware that they are HIV positive patients while 15 million persons are not being treated. This shows high inequality rates in the prevalence of HIV infection,

access to testing and treatment services despite the efforts made in putting the HIV epidemic to an end [6]. HIV inequality varies depending on sex, age, religion, education status, and region. The inequalities should be handled according to their socioeconomic factors. The sub-Saharan African region is affected greatly being the country with the highest number of HIV infections (5.5%) [6], hence a need for more attention. The importance of HIV testing cannot be overemphasized as this is the first step taken to knowing one's status and determining if further treatment and care are required or not. Lack of HIV screening will place the greater population at higher risk of new HIV infections [7]. Comprehensive sexuality education is crucial to resolving HIV inequalities hence putting an end to the HIV epidemic.

History of comprehensive sexuality education

Sexuality education has long existed for centuries right from the 1800s especially in the United States (US) and some western European countries [5, 8]. Sexuality education did not gain global recognition due to disagreement among many organizations, but as civilization, urbanization, and industrialization in the United States evolved, more attention was paid to it [9]. The US became the first country to initiate its first organizational body on sexuality education in 1905, called the American Society for Sanitary and Moral Prophylaxis, to reduce diseases associated with sexual contact [9]. After many decades, sexuality education grew tremendously and it gained public acceptance due to its importance and the information gotten from it; this instigated the move for this information to be addressed in homes, churches, and schools. As sexuality education continued to grow, it was then adopted by many other countries. It first began in Sweden in 1955 where it was added to school curriculum subject [5, 7], followed by many western European countries in the 1970s and 80s [5]. In Africa, CSE was taught in civics and hygiene classes and dated back as early as 1957 in Ghana [10]. The practice of sexuality education in schools continued to increase throughout the world. Today, sexuality education is an integral part of every educational system in the world.

Components of comprehensive sexuality education

There are seven essential components of comprehensive sexuality education namely; gender; sexual and reproductive health and HIV; sexual rights and sexual citizenship; pleasure; violence; diversity; relationship [10, 11].

- Gender: perceptions of gender roles should be understandable, knowing the difference between sex and gender. Having full knowledge of gender bias in the community and the consequences as a result of self-stigmatization.
- Sexual and reproductive health and HIV: this includes the sexuality of each gender starting from puberty to menopause, and sexual problems. Myths should be cleared out on virginity, sexual response, social expectations, and also having respect for the individual body. Understanding HIV and other sexually transmitted infections, including transmission and symptoms should be duly explained.
- Sexual rights and sexual citizenship: a rights-based approach to sexual and reproductive health, understanding that sexuality and culture are diverse and dynamic. Knowledge of international human rights and national policies, law, and structures that relate to people's sexuality.
- Pleasure: understanding that sex should be enjoyable and consensual, understanding that sex is much more than just sexual intercourse but a healthy and normal part of everybody's life; the biology and emotions behind the human sexual response; gender and pleasure; sexual wellbeing; safer sex practices and pleasure; masturbation; love, lust, and relationship.
- Violence: Gender-based violence should be explored with various types of violence toward men and women in the society and how they manifest; sex without the consent of two partners and understanding it is unjustifiable and unacceptable; laws and right; support options available and seeking help; community norms (power, gender) and myths; prevention, including personal safety plans; self-defence techniques.
- Diversity: Recognizing and understanding the range of diversity in our lives (e.g., faith, culture, ethnicity, socioeconomic status, ability/disability, HIV status, and sexual orientation); a positive view of diversity; recognizing discrimination, its adverse effects, and how to deal with it.
- Relationships: Recognizing that relationships are constantly changing, there are different types of relationships (e.g., family, friends, sexual romantic, etc.); those changes include emotions, intimacy (emotional and physical); rights and responsibilities; power dynamics; recognizing healthy and unhealthy or coercive relationships; communication, trust, and honesty in relationships; peer pressure and social norms; that love and sex are not the same.

The core principle of comprehensive sexuality education

Sexuality education has reasons for its establishment and formation, and these are expected to be met. Comprehensive Sexuality Education: Advancing Human

Rights, Gender Equality, and Improved Sexual and Reproductive Health highlighted the aims of sexuality education [5, 9, 11–13]. At the end of the information passed, the following must be met by CSE:

1. Intensity respect between individual and diversity;
2. Provide and strengthen young people in their participation to make decisions and critical thinking;
3. Encourage gender equality;
4. Communicate a positive, life-cycle approach to sexuality;
5. Entails information that has been scientifically proven;
6. Give a conducive and safe environment for ease of learning;
7. Including participatory teaching methods to help strengthen communication skills and decision-making abilities;
8. Address vulnerabilities, exclusion, and human rights violations, including gender-based violence and sexual abuse;
9. Gender and power issues should be addressed for better health outcomes in society.

Benefits of comprehensive sexuality education

Studies demonstrate that sexuality education provides many health benefits. Long-term sexuality education program reported in several European countries revealed a massive reduction in teenage pregnancies and abortion, decline in rates of sexually transmitted infections and HIV, increase self-confidence and invigorating skills to cope in different scenarios, empower young people to develop stronger and more meaningful relationships. Sexuality education has a positive impact on values and attitudes, and can even out the power dynamics in intimate relationships, contribution to the prevention of abuse and mutually respectful and consensual partnerships [10, 13], increased knowledge, sexual and reproductive issues normalization, and self-efficacy [14, 15].

Comprehensive sexuality education (CSE) and HIV

Human Immunodeficiency Virus (HIV) is a global health crisis with over 70 million people [16] who have been infected within and between the spheres of countries and regions of the world [17]. This deadly virus is one of the most persistent epidemics among humanity that attacks the antibodies responsible for fighting against a bodily harmful pathogen, thus making infections and diseases more vulnerable [17, 18]. In an immunodeficient person, the virus destroys and impairs the function of the immune cells responsible for fighting against diseases and infections. HIV as of present has no cure or vaccine to prevent its occurrence; once it is contracted, it goes on for a lifetime [19]. If left untreated, HIV advances to its last stage, Acquired Immunodeficiency Syndrome (AIDS) [20]. Despite the action to reduce the HIV prevalence with access to effective information, prevention, diagnosis, treatment, and care, it remains a major health concern and a chronic health condition that could only be managed by enabling people living with the condition a better, longer, and healthy life.

The prevalence of HIV among women accounts for more than half of the number of people living with HIV in the world. In 2016, it was recorded globally that women living with HIV were between the ages of 15 and above with an estimation of 17.8 million [19]. Today, AIDS-related illnesses are one of the leading causes of death for women between 15–49 years of age [20]. The population of Africa with HIV incidence is about 10% [20]. HIV prevalence among adults in the sub-Saharan part of Africa has reduced by more than half; there were approximately 1 million fewer new HIV infections from 2000 to 2012 [20]. McCutchan reported that young women are acquiring HIV five to seven years earlier than their male counterparts [21]. Young men of the same age as women (10–24 years) are half less likely to contract the incurable virus [22, 23].

Comprehensive sexuality education is core to sound physical, mental, and social well-being of health. CSE is said to be of good quality when the sexuality of men, fundamental human rights, gender equality, adolescent relationships, and reproductive sexual health education are met. Young people derive benefits from CSE as it provides adequate information needed to protect themselves from sexual infections, unwanted pregnancy, and HIV, thereby promoting the central principle of CSE including tolerance, mutual respect, and non-domestic relationship violence, not just that alone, but has a positive impact on safer sexual behaviours, delaying sexual debut and increasing condom use [15].

The prevention of HIV was incorporated into sexuality education internationally in the 1980s [24]. Globally, the proportion of adolescents infected is larger than that of adults. Worldwide, multiple sex partners and unprotected sexual intercourses are the main routes of transmission of HIV among young individuals. HIV-related risk is common among young people due to their engagement in illicit sex, transactional sex, multiple sex partners, sexual violence, rape, and coercion [25]. However, school-based sex education has been reported to promote awareness of HIV infection among young people and to curb the spread of the infection, just as reaching out to a large number of people through the

medium of a school-based intervention to equip and facilitate training, educational lessons, and group discussions for the young about their sexual activity and sexual life [26].

Gender inequality is an integral factor that affects increased HIV prevalence among young girls and women. UNESCO reported that this inequality among gender is linked to the decreased access of females to education or limited education and access to health information and services [27]. Many surveys have been conducted in different school environments on whether HIV prevention and sex education intervention among the youth is effective and whether it can be encouraged. A survey carried out on 758 students for 18 months showed that the introduction of reducing the risk curriculum (RTR) reduces the number of youth engaged in sexual intercourse during the 18 months, which reduced unprotected sex, either by increasing contraceptive use or delaying sexual intercourse. This survey shows that the knowledge of HIV-related risks and sexual behaviours is increasing, indicating that there is a chance of bridging the knowledge gap [26]. Kirby and Coyle concluded from their study that there is no significant association between abstinence and the delay of the sexual debut, while sexuality education was a potent means in bringing sexual risk to its minimum [28]. Speizer et al. reviewed a study on adolescent reproductive health intervention in developing countries. The study found that there is improved knowledge of HIV, its transmission, prevention, and management [28]. Findings made in examining comprehensive sexuality education status in over 48 countries globally revealed that 80% of the countries are working with strategies and policies that support comprehensive sexuality education; some countries, such as Latin America and the Caribbean, have signed a declaration to affirm HIV and school-based sexuality education. This study has further revealed that comprehensive sex education programs significantly reduce HIV, STI, and unintended pregnancies [25, 30].

Reshaping HIV inequality using comprehensive sexuality education

Joanne Herat, a senior program specialist in Health Education at UNESCO, reported that many regional and global policies still revealed significant gaps despite the effort of policymakers and political will [25]. Many organizations, including UNESCO, UNAIDS, UNFPA, WHO, and UN Women, came together to publish the International Technical Guidance on Sexuality Education in 2018. The sole aim of this guidance is to help decision- and policymakers create a precise and accurate curriculum for children and adolescents in their countries [26]. Furthermore, in 48 countries across the world, the CSE status was examined in a global review published by UNESCO, collaborated with UNAIDS Secretariat and United Nations Population Fund (UNFPA) in 2015 titled "Emerging Evidence Lesson and Practice in Comprehensive Sexuality Education". The report revealed that 80% of assessed countries have policies or strategies in place that support CSE [27]. Governments and stakeholders have targeted sexual health school-based education as a key strategy in reducing these issues to the lowest limit. Research also found that the teachers must be trained as it is for the effective delivery of CSE.

More so, many studies had proved that comprehensive sexuality education gives correct developmental, complete, accurate, and appropriate human sexuality information including risk-reduction strategies. In 2012, a study was conducted to access 66 sexual risk-reduction programs; the result of the study revealed that these programs are effective global health methods to bring about a reduction in adolescent HIV, STIs, and pregnancy [29]. Also, the national survey of Family Growth examined the effect and impact of sex education on youth between age 15–20, and it was found that teens who received the comprehensive sexuality education were about 50% less likely to experience pregnancy than those who were taught to abstain from sex until being married [31].

A study carried out by Euphemia et al. showed that the greater number of those tested in the past 12 months came from the poor and least educated, compared to the rich and educated. Knowledge of sexuality will encourage individuals to debunk myths, go for screening and be properly counselled [32].

Recommendations

1. Vulnerable adolescents such as the poor living in a rural communities, the uneducated, and sex workers cater to their needs, should be paid close attention [33] and properly counselled on how to survive without the abuse of one gender or the other;
2. Parents should try as much as possible to educate their children on a different part of their body and disease-associated to them, especially the genitals;
3. Schools should incorporate comprehensive sexuality education [34] in their curriculum;
4. The advocate must try as much as possible to break barriers to sexual health information and services including lack of health care facilities and poverty.

Conclusion

The population of people living with HIV keeps increasing daily; the prevalence of HIV infection is highest

in sub-Saharan African countries at 5.5%. This is a result of the inequalities in HIV prevention, testing, and management services. HIV inequality can be resolved by improving sexuality education. This can enlighten individuals on the basics of sexuality, their rights to their sexual health, the prevention of HIV and other STDs, and also reduce the stigmatization. Including CSE in both secondary and tertiary student's curriculum will greatly help in reducing HIV inequality.

Funding: *The study was self-funded.*

Conflict of interest: *Authors declare no conflicting interest.*

References

1. SIECUS State Profiles: Guidelines for Comprehensive Sexuality Education. Washington, DC: National guidelines task force, 3rd edition; SIECUS. ; 2004.
2. Keogh S, Stillman M, Leong E, et al. Measuring the quality of sexuality education implementation at the school level in low- and middle-income countries. Sex Education. 2019; 20(2): 119–137, doi: 10.1080/14681811.2019.1625762.
3. United Nations Population Fund. Comprehensive Sexuality Education. http://www.unfpa.org/comprehensive-sexuality-education (2020, November 30).
4. United Nations Educational, Scientific and Cultural Organisation. Why comprehensive sexuality education is important. https://en.unesco.org/news/why-comprehensive-sexuality-education-important (2020, November 30).
5. Bonjour M, van de. Comprehensive Sexuality Education: Knowledge File. Utrecht: Rutgers. ; 2018: 31p.
6. Challacombe SJ, Challacombe SJ. Global oral inequalities in HIV infection. Oral Dis. 2016; 22 Suppl 1: 35–41, doi: 10.1111/odi.12408, indexed in Pubmed: 27109270.
7. Cremin I, Cauchemez S, Garnett GP, et al. Patterns of uptake of HIV testing in sub-Saharan Africa in the pre-treatment era. Trop Med Int Health. 2012; 17(8): e26–e37, doi: 10.1111/j.1365-3156.2011.02937.x, indexed in Pubmed: 22943376.
8. European Expert Group on Sexuality Education. Sexuality education – what is it? Sex Education. 2015; 16(4): 427–431, doi: 10.1080/14681811.2015.1100599.
9. Herrman J, Solano P, Stotz L, et al. Comprehensive Sexuality Education: A Historical and Comparative Analysis of Public Opinion. American Journal of Sexuality Education. 2013; 8(3): 140–159, doi: 10.1080/15546128.2013.828342.
10. International Planned Parenthood Federation. Promoting comprehensive sexuality education in Ghana. https://www.ippfar.org/blogs/promoting-comprehensive-sexuality-education-ghana (2020, November 30).
11. United Nations Population Fund. Operational guidance for comprehensive sexuality education: a focus on human rights and gender. New York: UNFPA. ; 2014: 76p.
12. United Nations Population Fund. Comprehensive sexuality education: advancing human rights, gender equality and improved sexual and reproductive health. Bogota: UNFPA. ; 2010: 74p.
13. United Nations Educational, Scientific and Cultural Organisation. HIV and Sexuality Education. http://en.unesco.org/themes/health-education/hiv-sexuality-education (2020, December 1).
14. Rahmani A, Merghati-Khoei E, Fallahi A. Perceived Advantages and Disadvantages of Sex Education in Young Women: A Qualitative Study. International Journal of High Risk Behaviors and Addiction. 2018; 7(2), doi: 10.5812/ijhrba.57221.
15. Fonner VA, Armstrong KS, Kennedy CE, et al. School based sex education and HIV prevention in low- and middle-income countries: a systematic review and meta-analysis. PLoS One. 2014; 9(3): e89692, doi: 10.1371/journal.pone.0089692, indexed in Pubmed: 24594648.
16. Fajardo-Ortiz D, Lopez-Cervantes M, Duran L, et al. The emergence and evolution of the research fronts in HIV/AIDS research. PLoS One. 2017; 12(5): e0178293, doi: 10.1371/journal.pone.0178293, indexed in Pubmed: 28542584.
17. Centers for Disease Control and Prevention. About HIV. https://www.cdc.gov/hiv/basics/whatishiv.html (2020, December 3).
18. HIV.gov. What are HIV and AIDS? https://www.hiv.gov/hiv-basics/overview/about-hiv-and-aids/what-are-hiv-and-aids (2020, December 3).
19. UN WOMEN. Facts, and figures: HIV and AIDS. c2016. https://www.unwomen.org/en/what-we-do/hiv-and-aids/facts-and-figures (2020, November 30).
20. UNAIDS. Women and HIV — A spotlight on adolescent girls and young women. https://www.unaids.org/en/resources/documents/2019/women-and-hiv (2020, November, 30).
21. McCutchan FE. Global epidemiology of HIV. J Med Virology. 2006; 78(S1): S7–12.
22. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. J Int AIDS Soc. 2015; 18(2 Suppl 1): 19408, doi: 10.7448/IAS.18.2.19408, indexed in Pubmed: 25724504.
23. Avert. Women and girls, HIV and AIDS[Internet]. c2019. https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/women (2020, November 30).
24. Herrman J, Solano P, Stotz L, et al. Comprehensive Sexuality Education: A Historical and Comparative Analysis of Public Opinion. American Journal of Sexuality Education. 2013; 8(3): 140–159, doi: 10.1080/15546128.2013.828342.
25. Gallant M, Maticka-Tyndale E. School-based HIV prevention programmes for African youth. Soc Sci Med. 2004; 58(7): 1337–1351, doi: 10.1016/S0277-9536(03)00331-9, indexed in Pubmed: 14759680.
26. Kirby D, Coyle K. School-based Programs to Reduce Sexual Risk-taking Behavior. Children and Youth Services Review. 1997; 19(5-6): 415–436, doi: 10.1016/s0190-7409(97)00025-x.
27. Fonner VA, Armstrong KS, Kennedy CE, et al. School based sex education and HIV prevention in low- and middle-income countries: a systematic review and meta-analysis. PLoS One. 2014; 9(3): e89692, doi: 10.1371/journal.pone.0089692, indexed in Pubmed: 24594648.
28. Speizer IS, Magnani RJ, Colvin CE. The effectiveness of adolescent reproductive health interventions in developing countries: a review of the evidence. J Adolesc Health. 2003; 33(5): 324–348, doi: 10.1016/s1054-139x(02)00535-9, indexed in Pubmed: 14596955.
29. Sipe TA, Chin HB, Elder R, et al. Community Preventive Services Task Force, Community Preventive Services Task Force. The effectiveness of group-based comprehensive risk-reduction and abstinence education interventions to prevent or reduce the risk of adolescent pregnancy, human immunodeficiency virus, and sexually transmitted infections: two systematic reviews for the Guide to Community Preventive Services. Am J Prev Med. 2012; 42(3): 272–294, doi: 10.1016/j.amepre.2011.11.006, indexed in Pubmed: 22341164.
30. United Nations Educational, Scientific and Cultural Organisation. Global Review finds Comprehensive Sexuality Education key to gender equality and reproductive health. https://www.un.org/youthenvoy/2016/03/comprehensive-sexuality-education/ (2020, November 30).
31. Kohler PK, Manhart LE, Lafferty WE. Abstinence-only and comprehensive sex education and the initiation of sexual activity and teen pregnancy. J Adolesc Health. 2008; 42(4): 344–351, doi: 10.1016/j.jadohealth.2007.08.026, indexed in Pubmed: 18346659.
32. Sibanda EL, Taegtmeyer M. Inequalities in uptake of HIV testing despite scale-up. Lancet Glob Health. 2020; 8(6): e744–e745, doi: 10.1016/S2214-109X(20)30208-4, indexed in Pubmed: 32446337.
33. Olufadewa II, Adesina MA, Ayorinde TA. From Africa to the world: Re-imagining Africa's research capacity and culture in the global knowledge econony. Journal of Global Health. 2020; 10(1), doi: 10.7189/jogh.10.010321.
34. Adesina MA, Olufadewa II. Comprehensive Sexuality Education (CSE) curriculum in 10 East and Southern Africa Countries and HIV prevalence among the youth. European Journal of Environmental and Public Health. 2020, 4(1): em0035 https:doi.org/10.29333/ejeph/6009.

VIA MEDICA

REVIEW ARTICLE

Robert Gajda[1], Jacek Gajda[1], Miłosz Czuba[2,3], Anita Gębska-Kuczerowska[4], Beat Knechtle[5,6]

[1]Center for Sports Cardiology, Gajda-Med Medical Centre in Pultusk, Pultusk, Poland
[2]Department of Applied and Clinical Physiology, Collegium Medicum University of Zielona Gora, Zielona Gora, Poland
[3]Department of Kinesiology, Institute of Sport, Warsaw, Poland
[4]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszyński University, Warsaw, Poland
[5]Institute of Primary Care, University of Zurich, Zurich, Switzerland
[6]Medbase St. Gallen Am Vadianplatz, St. Gallen, Switzerland

Heart rate monitors used by athletes — from gadget to medical equipment. A decade of own observations

Corresponding author:

Robert Gajda, Centre for Sports Cardiology, Gajda-Med Medical Centre in Pultusk, Piotra Skargi 23/29 Str., 06-100 Pultusk, Poland, e-mail: gajda@gajdamed.pl

Medical Research Journal 2021; Volume 6, Number 1, 64–70
10.5603/MRJ.a2021.0010

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: For many years, many athletes have reported to the Centre for Sports Cardiology in Pultusk that during endurance training, mainly running and cycling, they found unexpected increases in heart rate (HR) values observed on sports heart rate monitors (HRMs), in the vast majority of cases without the accompanying clinical symptoms. The authors have attempted to answer the question of whether the "arrhythmia" observed on HRMs is a rhythm disturbance or a mere technical artefact. This article aimed to summarize the authors' observations in the field of the usefulness of HRMs for the assessment of cardiac arrhythmias in the situation of introducing new technological solutions in the modernized and enriched ones with new functions HRMs.

Material and methods: Over ten years, numerous studies have been carried out and the world literature has been also analysed many times, finally describing the authors' study results and observations in numerous types of English-language articles published between 2017 and 2021.

In this review article, the authors focused only on their publications from the Centre for Sports Cardiology in Pultusk on the issues of heart rhythm disturbances observed on HRMs by endurance athletes, and on publications in which researchers from CKS participated and the articles themselves were related with the use of HRMs. Only a few references have been cited from other sources.

Conclusions: The HRMs used in the past years were not significant for the treatment of asymptomatic exercise-stimulated arrhythmias. These HRMs, however, in a symptomatic arrhythmia situation, became an effective diagnostic tool confirming its occurrence. The analysis of cases and literature shows that modern sports heart rate monitors used by athletes of endurance disciplines (especially with the possibility of ECG recording) are becoming a useful, important and more and more effective diagnostic tool in the detection and final diagnosis of cardiac arrhythmias stimulated by exercise, both symptomatic and asymptomatic athletes and can significantly contribute to the increase of safety during training. It can be assumed that future HRMs will have comparable diagnostic value in detecting cardiac arrhythmias as the Holter ECG, surpassing them with the possibility of constant data transmission, ease of use and affordable price.

Key words: arrhythmia, supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, endurance athletes, atrioventricular nodal re-entrant tachycardia (AVNRT), commotio cordis, heart rate monitors, exertion rhythm disorders

Med Res J 2021; 6 (1): 64–70

Material and methods

This review article uses manuscripts created almost exclusively (mostly) based on own experience related to the use of HRMs and published by researchers co-operating with the Sports Cardiology Centre in Puŀtusk. The articles used in this manuscript mainly concerned the published results of own research, observations and analyses of the literature on the use of HRMs to control heart rhythm and the identification of potential post-exercise arrhythmia mainly among endurance athletes. The article also includes its own observations (published articles) on rehabilitated and treated patients with cardiovascular diseases using HRMs to control heart rhythm.

Inclusion criteria for literature selection, apart from those already mentioned (own observations), were the following keywords: arrhythmia, supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, endurance athletes, Atrioventricular Nodal Re-entrant Tachycardia (AVNRT), Commotio Cordis, heart rate monitors (HRMs), exertion rhythm disorders.

Exclusion criteria for literature selection: listed keywords (for own articles) but articles not relevant for article review.

Results and discussion

The usefulness of sports heart rate monitors in diagnosing arrhythmia in asymptomatic and symptomatic athletes

Millions of physically active individuals worldwide use heart rate monitors (HRMs) to monitor their exercise intensity. In many cases, HRMs may indicate an unusually high heart rate (HR) or even arrhythmias during training. Unfortunately, few studies existed that assessed the reliability of these devices in monitoring HR disturbances during exercise.

The observation was started in 2011. After preparing methods 142 regularly training endurance runners and cyclists were examined, aged 18–51 years, with unexplained HR abnormalities indicated by various HRMs to assess the utility of HRMs in diagnosing exertion-induced arrhythmias. Each athlete simultaneously wore a Holter electrocardiogram (ECG) recorder and an HRM during typical endurance training in which they had previously detected "arrhythmias", to verify the diagnosis. Average HRs during exercise were precisely recorded by all types of HRMs. No signs of arrhythmia were detected during exercise in approximately 39% of the athletes, and concordant HRs were recorded by the HRMs and Holter ECG. Surprisingly, high short-term HRs were detected by HRMs in 45% of the athletes, but not by the Holter ECG and were considered artefacts. In 15% of the athletes, single ventricular/supraventricular beats were detected by the Holter ECG but not by the HRM. In one athlete was detected a serious tachyarrhythmia via both the HRM and Holter ECG with concomitant clinical symptoms; this athlete was forced to cease exercising (Holter ECG examination revealed atrioventricular nodal reentrant tachycardia [AVNRT]). It was concluded that the HRM is not a suitable tool for monitoring heart arrhythmias in athletes and proposed an algorithm to exclude the suspicion of exercise-induced arrhythmia detected by HRMs in asymptomatic, physically active individuals [1, 2].

Having information about the usefulness of HRMs in the diagnosis of asymptomatic arrhythmias, another research was started (actually continued the previous one) completed after 6 years of observation, on their usefulness in the situation of symptomatic athletes (triathlete) with suspicion of arrhythmia. This case study described triathlete in whom HRM showed high HR values during exercise and clinical symptoms forced him to stop training (AVNRT in Holter ECG and the same HR on HRMS at this moment) during the first study.

This case study completed finally in 2020, described a triathlete with effort-provoked AVNRT diagnosed 6 years prior, who ineffectively controlled his training load via HRMs to avoid tachyarrhythmia. Of the 1800 workouts recorded over 6 years via the HRMs, 45 tachyarrhythmias were found, which forced the athlete to stop exercising. In three of them, AVNRT was simultaneously confirmed by a Holter ECG. Tachyarrhythmias occurred at different phases (after the 2nd–131st minutes, median: 29th minute) and frequencies (3–8, average: 6.5 times/year), characterized by different HRs (150–227 beats per minute (bpm), median: 187 bpm) and durations (10–186, median: 40 s). Tachyarrhythmia appeared unexpectedly in the initial stages of training, as well as quite predictably, during prolonged submaximal exercise but without rigid rules. Tachyarrhythmias during cycling were more intensive (200 *vs.* 162 bpm, $p = 0.0004$) and occurred later (41 *vs.* 10 min, $p = 0.0007$) than those during running (the only one noticed but not recorded during swimming). A tendency was noticed ($p = 0.1748$) towards the decreasing duration time of tachycardias (2014–2015: 60 s; 2016–2017: 50 s; 2018–later: 37 s). The amateur athlete tolerated the tachycardic episodes quite well, and the ECG test and echocardiography were normal. In this studied case, the HRM was a useful diagnostic tool for detecting symptomatic arrhythmia; however, no change in the amount, phase of training, speed, or duration of exercise-stimulated tachyarrhythmia was observed [3].

The above studies showed that the HRMs used in the past years were not useful in detecting asymptomatic exercise-stimulated arrhythmias. However, in the event of symptomatic arrhythmia, these HR monitors became an effective diagnostic tool for confirming its occurrence. None of the HRMs used in these studies

had an ECG recording function, a feature that is slowly emerging in modern HRMs.

Sports HRMs — how do they work and why are they indispensable for athletes, especially in endurance sports?

The key to effective training of endurance athletes in disciplines such as the triathlon, cycling, and long-distance running is to perform the training within a specific range of HR values. For this reason, HRMs have become an indispensable tool for athletes in achieving their training objectives [4]. HR is a useful indicator of physiologic adaptation and effort intensity. Therefore, HR monitoring is an important component of cardiovascular fitness assessments and training programs [5]. Similar to conventional ECG devices, the HRMs used by athletes determine their HRs by receiving the main electrical field produced by the heart muscle through electrodes placed on a transmitter belt attached to the chest; the signal is then transmitted by a probe to a digital recorder, most commonly a special wristwatch, via telemetry. Thus, an HRM may also function as a Global Positioning System. In recent years, the extensive use of sports HRMs by cardiac patients performing physical activities was observed, particularly running and cycling, as primary and secondary methods for preventing cardiovascular diseases, including coronary heart disease and hypertension [6]. HRMs have been designed for use by healthy athletes with a baseline sinus rhythm, but they also capture exercise-induced arrhythmia [7]. However, information about the morphology of the QRS complex has not been reported, and atrial signals have not been detected [8]. During medical consultations at the Centre for Sports Cardiology in Pułtusk, doubts repeatedly arose regarding the reliability of results generated by HRMs during running or cycling training that suggested an "arrhythmia," particularly in situations where clinical symptoms were not observed and when only unspecified symptoms typical of an anxiety disorder were observed [1].

With the increasing popularity of the use of HRMs by athletes and cardiac patients using running or cycling as primary and secondary methods for preventing cardiovascular diseases and because of the many reports of suspected arrhythmia based on HRM indications, several systematic investigations among Centre for Sports Cardiology study participants were initiated, testing "old" and "modern" HRMs [3].

History of HRMs — from "fingers on the radial artery" to advanced ECG recording technologies

The first reports of commercial medical devices for measuring HR were published at the beginning of the 18th century [9]. Partially reliable HR control during training appeared with the widespread introduction of sweep hand watches more than 200 hundred years ago. The athlete had to stop and count their pulse on the radial artery for 10 seconds and then multiply this number by 6 to determine their HR. In this way, they obtained their HR value at the peak of exercise, allowing them to determine the load in the last phase. There was no opportunity to determine the average HR during training; thus, exercise intensity could not be evaluated as a whole.

All HRMs today record HR; however, this is not enough to establish a complete diagnosis of the origin of the rhythm and potential threats to the life and health of the athlete when pathological. There is no facility to determine whether an arrhythmia at a given time is caused by numerous harmless supraventricular beats – or atrial fibrillation – or whether it is a life-threatening ventricular tachycardia [10, 11]. The ability to measure HR in water was another important step, enabling swimmers and triathletes to monitor their training, although without the possibility of recognizing the source of the "beat" in HRMs (sinus rhythm, supraventricular or ventricular beats, etc.) [12, 13].

Commonly used strap HRMs (SHRMs), which have been commercially available for many years, indicate the correct HR value; however, in the event of an arrhythmia, they are still not a reliable source of information about its type. The introduction of the Heart Rate Variability assessment function to HRMs has allowed rhythm "regularity" to be determined; however, it is unable to determine whether a regular or complete arrhythmia is the result of supraventricular/ventricular beats or ordinary artefacts [10]. SHRMs assess the main electric field produced during ventricle contraction. Therefore, they estimate the distance of the R-R points without identifying either P-wave morphology or the QRS complex [14]. This function is completely inadequate in the case of commotio cordis, the mortality rate of which—regardless of the type of HRM or the device controlling the workings of the heart (except for the cardioverter-defibrillator)—is very high. However, healthy athletes do not have access to cardioverter-defibrillators [15].

Optical HRMs (OHRMs) have been on the market for about 10 years. The principle of their operation is common, and the accuracy of their measurements is similar to that of the chest SHRM. Optical pulse monitors operate under a completely different principle than SHRMs. While SHRMs work similarly to ECGs, OHRMs use a phenomenon called photoplethysmography, which constitutes transmission of light through the skin and measurement of the amount of light that is scattered by blood flow. Photoplethysmography sensors are based on the fact that light entering the body will scatter predictably as the blood flow dynamics change, such as with changes in the blood pulse rate or with changes in blood volume (cardiac output). In practice,

the optical HR sensor located on the underside of the watch illuminates the blood vessels in the wrist tissue using LEDs, measuring the amount of light dispersed by the blood flow. The advantage of a wrist pulse measurement is convenience, i.e., the ability to measure HR without having to wear a separate strap or other sensors to measure the pulse. Such a watch must be placed directly on the skin with no material in between; occasionally, the watch must be worn higher on the wrist than a normal wristwatch. The sensor detects blood flow through the blood vessels; therefore, the tissue thickness determines the measurement accuracy [16].

OHRMs can only determine rhythm regularity and, thus, can indirectly be used to make diagnoses e.g., complete arrhythmia—suspicion of atrial fibrillation [17].

The use of smartphones for arrhythmia monitoring is another advancement for ECG utilization and arrhythmia detection, effectively making the technology available to any smartphone user. Smart wearable technology, while very common, is mostly limited to activity tracking and exercise motivation. Rhythm-strip-generating smartphone products, such as Kardia Mobile by AliveCor and ECG Check by Cardiac Designs, can more accurately detect arrhythmias than wearable monitors. These products, which have been studied in a variety of situations, rely on the use of an external device with metal sensors to create a rhythm strip, which is usually Lead I. A different subset of smartphone products utilizes photoplethysmography through a phone camera and light to detect atrial fibrillation. Together, these products have created a paradigm shift in rhythm detection and monitoring [18].

New electrodes built into the back crystal and digital crown on the Apple Watch Series 4 work together with the ECG app to enable customers to produce an ECG recording similar to a single-lead reading. To take an ECG recording at any time, or following an irregular rhythm notification, users launch the new ECG app on Apple Watch Series 4 and hold their finger on the digital crown. As the user touches the digital crown, the circuit is complete and electrical signals across the heart are measured. After 30 seconds, the heart rhythm is classified as either AFib, sinus rhythm, or inconclusive. All recordings, their associated classifications, and any noted symptoms are stored securely in the Health application of the iPhone. Users can share a PDF of their results with physicians. Although similar to the Apple Watch, it is only a record of one limb lead, and it can clearly recognize both the P-wave and the QRS complex. This fully corresponds to the classic single Lead 1 ECG recording. The biggest disadvantage of this function is that activity must be paused for the recording, contradicting the idea of measurement during training [19].

However, technological advancements brought new solutions including HRMs with applications enabling constant ECG recording during training to the market. The QardioMD system (namely, QardioCore ECG with QardioMD remote monitoring cloud-based portal) can be described as a typical strap HRM with the difference that the information from the transmitter (strap) is transferred to the Qardio mobile app on the iPhone, i.e., the receiver. After a delay of about 3 minutes, information from the iPhone is transmitted to the "cloud." The downloading of information to the Monitoring Centre (Hospital, Clinic with QardioMD remote monitoring cloud-based portal) allows ECG control, which is continuously recorded, and automatic recognition of life-threatening heart rhythm disorders. The inconvenience of carrying a phone during training is minor considering the enormous amount of information obtained and stored. The Monitoring Centre offers an ECG recording with three limb leads (modified leads I, II, III) with automated arrhythmia detection, QRS morphology analysis, P-wave detection (for enhanced automated AF detection), and the possibility of manually assessing PQ, QT, and ST segments. It is a matter of time until an automatic diagnosis of stress ischaemia with the QardioMD system will become available. Preliminary studies have shown that it is a system with comparable diagnostic value to the standard 3 Lead Holter ECG monitor [20].

Strap HRMs or optical HRM?

The surveyed athletes, coaches, and physicians answered this question unequivocally [18]. OHRMs, provided that their indications are reliable, are preferred. Wearing a chest strap is troublesome for athletes for numerous reasons, ranging from battery depletion artefacts, interference in the transmission between the strap and the receiver, to the most important for ultramarathon runners: chafing of the skin during long hours of running by a moving strap [21]. It is also common to simply forget to put it on during training, which significantly changes the subsequent evaluation of training. Therefore, OHRMs are preferred on the condition that the accuracy of their indications, which remains a problem, is improved [21]. In the past, the inability to measure HR by HRMs in the water was an issue, which was a significant limitation for triathletes and swimmers; however, this problem has now been resolved [12]. OHRMs usually also have a longer battery life which, in 24- or 48-hour ultramarathons, is of great importance [22]. It is important to note that there are still outstanding endurance runners who, for mental reasons, do not use an HRM during competition [23, 24].

Will HRMs replace the Holter ECG?

Sports HRMs were introduced to monitor HR values in healthy athletes and were not meant to be or compete with medical devices [25]; however, it is impossible to run daily with an ECG Holter to verify periodic indications of incorrect values while training with an HRM. An algorithm has been developed to deal with such cases [16]. Nevertheless, HRMs should be considered as devices with useful and reliable medical functions, such as reliable ECG recording, intended for use by athletes. Today's ECGs recorded by HRMs are single limb lead recordings (Apple Watch) or, as in the case of the QardioMD system, a 3-limb lead recording. However, this is an evolutionary advancement, introducing devices "for measuring HR for healthy athletes" as advanced medical diagnostic tools for use in sports cardiology [26].

The trouble-free use of HRMs in everyday life makes them a candidate for use as professional equipment that requires special handling skills and professional knowledge for result interpretation (e.g., Holter ECG). It seems that it will only be a matter of time before HRMs will be able to record a 12-lead ECG with the possibility of assessing all ECG features, including the ST segment, which will be extremely important for the diagnosis of exercise ischaemia in a classic exercise test [27]. Other data, such as measuring the QT interval or identifying the origin of ventricular beats, will become automatic information related to these recordings.

Anyone, including potentially healthy top athletes, may experience life-threatening exercise arrhythmias [28]. The registration and early interpretation by the HRMs used today by millions of active people may save lives in the future.

It seems that, in the future, the increasingly perfect ECG data recorded on a typical sports HRM will lead to these devices being treated as medical devices necessary for safe, highly professional, and recreational training. The usefulness of these devices in cardiac rehabilitation is undisputed [29].

Currently, a long-term observational study of patients with long QT syndrome type VII is performed, employing modern HRMs (with long "battery life") for use in ultramarathoners [30, 31].

Bradycardia and bradyarrhythmia in athletes ,,caught" on HRMs?

Tachyarrhythmias are mentioned constantly, regarding the usefulness of HRMs in the assessment of cardiac arrhythmias; however, wearing HRMs – as in the case of OHRMs – may contribute to the registration of not only fast rhythms during training but also night bradyarrhythmias, which are common rhythm disturbances in athletes of endurance disciplines [32]. Undoubtedly, this is a space where HRMs, which are used by many athletes, can contribute both to the diagnosis of arrhythmias – if data are "recorded continuously" – and data collection. All existing HRM models register a decrease in HR, but they do not all recognize the mechanism by which this decrease occurs (either a conduction block or ordinary bradycardia). In asymptomatic and apparently healthy athletes, either at rest or during sleep, even 15-second pauses in the Holter ECG examination are common. Northcote et al. examined 20 male veteran endurance runners who underwent resting, exercise, and ambulatory electrocardiography testing; six athletes had a first-degree heart block, four had a Mobitz II second-degree block, and three had a complete heart block [33].

The "athlete's heart" and its accompanying bradycardia, or the second-degree A-V block, are physiological adaptations to exercise; however, a break of a few seconds is certainly a pathology that has the potential to be increasingly recognized by athletes using HRMs both in training and at rest and/or sleep. Comfort is also the reason why OHRMs seem to be a more common direction of development [34].

Perspectives — directions of HRMs development

The future of HRMs includes improvement in the accuracy of already-existing indications, in addition to the development of new technology that will allow the widespread use of OHRMs with the function of 24-hour ECG recording. Moreover, athletes, coaches, and doctors are interested in other functions that are not yet available today, such as the expected oxygen threshold indicator. Certainly, new solutions will be presented, other than the ones currently available, allowing not only trouble-free ECG recording during training, but also the ability to inform the athlete, coach, or doctor via online means regarding any potential threats in the form of heart rhythm disturbances, as well as the emerging features of stress ischaemia.

This is important to increase the awareness of athletes regarding the need to protect their health during training by controlling heart rhythm and not just HR (i.e., ECG recording). Furthermore, to protect the lives and health of athletes who sometimes experience tragic cardiac arrhythmias triggered by exercise, the widespread use of HRMs with continuous ECG recording should be encouraged in the future.

Conclusions and practical applications

The HRMs used over the past years were not shown to be useful in the detection of asymptomatic exercise-stimulated arrhythmias. However, these

HRMs were effective diagnostic tools in confirming the occurrence of symptomatic arrhythmia. The analyses of cases and review of the literature show that modern sports HRMs used by endurance sport athletes are becoming a useful, important, and more effective diagnostic tool in the detection and final diagnosis of exercise-stimulated cardiac arrhythmias, which may contribute to the increase in safety of both symptomatic and asymptomatic athletes during training. It can be assumed that future HRMs will have comparable diagnostic value in detecting cardiac arrhythmias as the Holter ECG, surpassing them with the possibility of constant data transmission, ease of use and affordable price.

List of abbreviations: HR — heart rate; HRMs — heart rate monitors; ECG — electrocardiogram; AVNRT — atrioventricular nodal reentrant tachycardia; SHRM — strap heart rate monitor.

Acknowledgements: *This research received no external funding.*

Conflicts of interest: *The authors declare no conflict of interest.*

Author contributions: *R.G. conceived of and designed the article; created the final version. JG, MC, A G-K and BK analysed and chose the bibliography used in the article; corrected the article before submission to the editorial office. R.G. answered questions from reviewers and wrote the final version of the paper. All authors have read and agreed to the published version of the manuscript.*

References

1. Gajda R, Biernacka EK, Drygas W. Are heart rate monitors valuable tools for diagnosing arrhythmias in endurance athletes? Scand J Med Sci Sports. 2018; 28(2): 496–516, doi: 10.1111/sms.12917, indexed in Pubmed: 28543790.
2. Gajda R. Relationship Between Arrhythmias and Level Activity of Athlete's-Role of HRMs. Examines in Physical Medicine & Rehabilitation. 2019; 2(5), doi: 10.31031/epmr.2019.02.000548.
3. Gajda R. Heart Rate Monitor Instead of Ablation? Atrioventricular Nodal Re-Entrant Tachycardia in a Leisure-Time Triathlete: 6-Year Follow-Up. Diagnostics (Basel). 2020; 10(6), doi: 10.3390/diagnostics10060391, indexed in Pubmed: 32532026.
4. Terbizan D, Dolezal B, Albano C. Validity of Seven Commercially Available Heart Rate Monitors. Measurement in Physical Education and Exercise Science. 2002; 6(4): 243–247, doi: 10.1207/s15327841mpee0604_3.
5. Laukkanen RM, Virtanen PK. Heart rate monitors: state of the art. J Sports Sci. 1998; 16 Suppl: S3–S7, doi: 10.1080/026404198366920, indexed in Pubmed: 22587712.
6. Lavie CJ, Thomas RJ, Squires RW, et al. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. Mayo Clin Proc. 2009; 84(4): 373–383, doi: 10.1016/S0025-6196(11)60548-X, indexed in Pubmed: 19339657.
7. Müssigbrodt A, Richter S, Wetzel U, et al. Diagnosis of arrhythmias in athletes using leadless, ambulatory HR monitors. Med Sci Sports Exerc. 2013; 45(8): 1431–1435, doi: 10.1249/MSS.0b013e31828ca1bf, indexed in Pubmed: 23470304.
8. Hunt D, Tanto P. Diagnosis of arrhythmias in athletes wearing heart rate monitors. J R Army Med Corps. 2017; 163(3): 224, doi: 10.1136/jramc-2016-000696, indexed in Pubmed: 27811196.
9. Pulse watch. https://en.wikipedia.org/wiki/Pulse_watch (11 March 2021).
10. Gajda R. Ventricular Arrhythmias in Endurance Athletes. Are Heart Rate Monitors Suitable Tools for their Diagnostics? Research & Investigations in Sports Medicine. 2019; 5(4), doi: 10.31031/rism.2019.05.000622.
11. Gajda R. Atrial Fibrillation in Athletes-Easier to Recognize Today? Research & Investigations in Sports Medicine. 2019; 5(4), doi: 10.31031/rism.2019.05.000618.
12. Gajda R, Kowalik E, Rybka S, et al. Evaluation of the Heart Function of Swimmers Subjected to Exhaustive Repetitive Endurance Efforts During a 500-km Relay. Front Physiol. 2019; 10: 296, doi: 10.3389/fphys.2019.00296, indexed in Pubmed: 30967795.
13. Nowak M, Gajda R, Drygas W, et al. Effect of repeated endurance exercise on intraocular pressure in healthy subjects: a prospective pilot study based on a 500-km swim relay. Klinika Oczna. 2020; 2020(2): 54–59, doi: 10.5114/ko.2020.96557.
14. Giles DA, Draper N. Heart Rate Variability During Exercise: A Comparison of Artefact Correction Methods. J Strength Cond Res. 2018; 32(3): 726–735, doi: 10.1519/JSC.0000000000001800, indexed in Pubmed: 29466273.
15. Gajda R. Commotio Cordis at Athletes–Under Recognized Problem. Research & Investigations in Sports Medicine. 2019; 5(3), doi: 10.31031/rism.2019.05.000615.
16. Gajda, R, Biernacka, E.K, Drygas, W. The problem of arrhythmias in endurance athletes: are heart rate monitors valuable tools for diagnosing arrhythmias? In Horizons in World Cardiovascular Research. Bennington, H.B. , Eds; Nova Science Publishers: New York, USA, 2009; Volume 15, pp. : 1–64.
17. Gajda R. Atrial Fibrillation in Athletes-Easier to Recognize Today? Research & Investigations in Sports Medicine. 2019; 5(4), doi: 10.31031/rism.2019.05.000618.
18. Gajda R. Is Continuous ECG Recording on Heart Rate Monitors the Most Expected Function by Endurance Athletes, Coaches, and Doctors? Diagnostics (Basel). 2020; 10(11), doi: 10.3390/diagnostics10110867, indexed in Pubmed: 33114156.
19. Massoomi MR, Handberg EM. Increasing and Evolving Role of Smart Devices in Modern Medicine. Eur Cardiol. 2019; 14(3): 181–186, doi: 10.15420/ecr.2019.02, indexed in Pubmed: 31933689.
20. Barr, C. Comparison of Accuracy and Diagnostic Validity of a Novel Non-Invasive Electrocardiographic Monitoring Device with a Standard 3 Lead Holter Monitor and an ECG Patch over a 24 hours Period. J Cardiovasc Dis Diagn. 2019; 7: 5.
21. Gajda R, Klisiewicz A, Matsibora V, et al. Heart of the World's Top Ultramarathon Runner-Not Necessarily Much Different from Normal. Diagnostics (Basel). 2020; 10(2), doi: 10.3390/diagnostics10020073, indexed in Pubmed: 32012817.
22. Optical HR Armband Shootout: Polar OH1+, Scosche Rhythm 24, Wahoo TICKR FIT. https://www.dcrainmaker.com/2019/04/optical-heart-rate-sensor-armband-shootout-schosche24-polaroh1-wahoo-tickr-fit.html (11 March 2021).
23. Gajda R, Walasek P, Jarmuszewski M. Right Knee-The Weakest Point of the Best Ultramarathon Runners of the World? A Case Study. Int J Environ Res Public Health. 2020; 17(16), doi: 10.3390/ijerph17165955, indexed in Pubmed: 32824529.
24. Gajda R, Samełko A, Czuba M, et al. To Be a Champion of the 24-h Ultramarathon Race. If Not the Heart ... Mosaic Theory? International Journal of Environmental Research and Public Health. 2021; 18(5): 2371, doi: 10.3390/ijerph18052371.
25. Bircher S, Enggist A, Jehle T, et al. Effects of an extreme endurance race on energy balance and body composition - a case study. J Sports Sci Med. 2006; 5(1): 154–162, indexed in Pubmed: 24198693.
26. Garabelli P, Stavrakis S, Po S. Smartphone-based arrhythmia monitoring. Curr Opin Cardiol. 2017; 32(1): 53–57, doi: 10.1097/HCO.0000000000000350, indexed in Pubmed: 27875477.
27. Marcadet DM, Pavy B, Bosser G, et al. French Society of Cardiology guidelines on exercise tests (part 1): Methods and interpretation. Arch Cardiovasc Dis. 2018; 111(12): 782–790, doi: 10.1016/j.acvd.2018.05.005, indexed in Pubmed: 30093254.
28. Biffi A, Maron BJ, Di Giacinto B, et al. Relation between training-induced left ventricular hypertrophy and risk for ventricular tachyarrhythmias in elite athletes. Am J Cardiol. 2008; 101(12): 1792–1795, doi: 10.1016/j.amjcard.2008.02.081, indexed in Pubmed: 18549861.

29. Szczepańska-Gieracha J, Jóźwik S, Cieślik B, et al. Immersive Virtual Reality Therapy As a Support for Cardiac Rehabilitation: A Pilot Randomized-Controlled Trial. Cyberpsychol Behav Soc Netw. 2021 [Epub ahead of print], doi: 10.1089/cyber.2020.0297, indexed in Pubmed: 33577375.
30. Krych M, Biernacka EK, Ponińska J, et al. Andersen-Tawil syndrome: Clinical presentation and predictors of symptomatic arrhythmias - Possible role of polymorphisms K897T in KCNH2 and H558R in SCN5A gene. J Cardiol. 2017; 70(5): 504–510, doi: 10.1016/j.jjcc.2017.01.009, indexed in Pubmed: 28336205.
31. Jagodzińska M, Szperl M, Ponińska J, et al. Coexistence of Andersen-Tawil Syndrome with Polymorphisms in hERG1 Gene (K897T) and SCN5A Gene (H558R) in One Family. Ann Noninvasive Electrocardiol. 2016; 21(2): 189–195, doi: 10.1111/anec.12283, indexed in Pubmed: 26109178.
32. Doyen B, Matelot D, Carré F. Asymptomatic bradycardia amongst endurance athletes. Phys Sportsmed. 2019; 47(3): 249–252, doi: 10.1080/00913847.2019.1568769, indexed in Pubmed: 30640577.
33. Northcote RJ, Canning GP, Ballantyne D. Electrocardiographic findings in male veteran endurance athletes. Br Heart J. 1989; 61(2): 155–160, doi: 10.1136/hrt.61.2.155, indexed in Pubmed: 2923752.
34. Gajda R. Extreme Bradycardia and Bradyarrhythmias at Athletes. What will Technology Development Bring as a Help to Diagnosis Them? Research & Investigations in Sports Medicine. 2019; 5(4), doi: 10.31031/rism.2019.05.000617.

VIA MEDICA

CASE REPORT

Marcin Kleibert[1], Małgorzata Wojciechowska[1,2], Maciej Zarębiński[2], Łukasz Pastwa[3], Agnieszka Cudnoch-Jędrzejewska[1]

[1]Department of Experimental and Clinical Physiology, Laboratory of Center for Preclinical Research, Medical University of Warsaw, Warsaw, Poland
[2]Independent Public Specialist Western Hospital John Paul II, Invasive Cardiology Unit, Grodzisk Mazowiecki, Poland
[3]Independent Public Specialist Western Hospital John Paul II, Cardiology Unit, Grodzisk Mazowiecki, Poland

Multiple cardiac arrests due to Lyme carditis

Corresponding author:

Małgorzata Wojciechowska, Department of Experimental and Clinical Physiology, Laboratory of Center for Preclinical Research, Medical University of Warsaw, Warsaw, Poland, e-mail: mwojciechowska2@wum.edu.pl

Medical Research Journal 2021; Volume 6, Number 1, 71–74
10.5603/MRJ.a2021.0002

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

The most common form of Lyme carditis (LC) are different types of conduction abnormalities, especially atrioventricular (A-V) blocks. In most cases the course of the disease is benign and when the patient is diagnosed and treated appropriately, even the most advanced forms of A-V block typically resolve within one week. Implantation of a permanent pacemaker is only exceptionally necessary.

We present a case of a patient with multiple cardiac arrests due to advanced A-V block. Despite the proper diagnosis of LC and targeted antibiotic therapy, the patient was completely dependent on temporary endocavitary pacing for more than one week. Finally, implantation of a permanent pacemaker was decided, however, during the next three months, A-V conduction abnormalities gradually subsided. This made us doubt whether the decision about implantation wasn't made prematurely. The solution came at a one-year follow-up visit when it turned out that ventricular stimulation reappeared.

We believe, that if A-V conduction disturbances in the course of Lyme disease persist for more than a week despite targeted antibiotic therapy, it is most likely a sign of serious and irreversible damage to the structures of the A-V node.

Key words: permanent pacemaker, complete atrioventricular block, Lyme disease

Med Res J 2021; 6 (1): 71–74

Introduction

Lyme disease (LD) is one of the most common tick-borne diseases. Etiologic factors are species of spirochetes (Borellia afzelli, B. garini, B. burgdorferi), which are the Gram-negative bacteria. The incubation period from infection to the onset of symptoms is usually 1–2 weeks. The first and most common presentation of the disease is erythema chronicum migrans (early localized phase, stage 1), which is seen in 70–90% of patients. It may be accompanied by unspecific symptoms of infection, such as muscle pain, fever and headache. During the next weeks occupation of different organs and systems may develop (early disseminated phase, stage 2), with most frequent affection of the skin, joints and nervous system. Chronic phase (late disseminated phase, stage 3) occurs after 2–3 years and most commonly refers to neurological and rheumatological complications [1–3].

Lyme carditis (LC) develops in less than 5% of patients infected, with a visible male predominance (3:1). The cardiovascular signs occur in early disseminated disease (stage 2), usually in the third week after infection, however, they may appear between the 7th day and the 7th month of the illness. The pathophysiology involves infiltration of bacteria and subsequent excessive immunologic response, mainly in the connective tissue of the basal part of the interventricular septum. The majority of the cases are conduction abnormalities (90%), mostly atrioventricular (A-V) blocks, however, pericarditis, myocarditis, cardiomyopathy and degenerative valvular disease have been occasionally observed [2, 4, 5].

If the infectious agent is identified and treated appropriately, even advanced forms of conduction abnormalities have a benign prognosis and disappear quickly, usually during one week [4]. Hospitalization and continuous cardiac monitoring are recommended for patients with second- or third-degree A-V block, first-degree A-V block with a PR interval >300 ms and fluctuating bundle branch blocks.

The treatment of choice is intravenously administered antibiotics, preferably ceftriaxone, however, cefu-

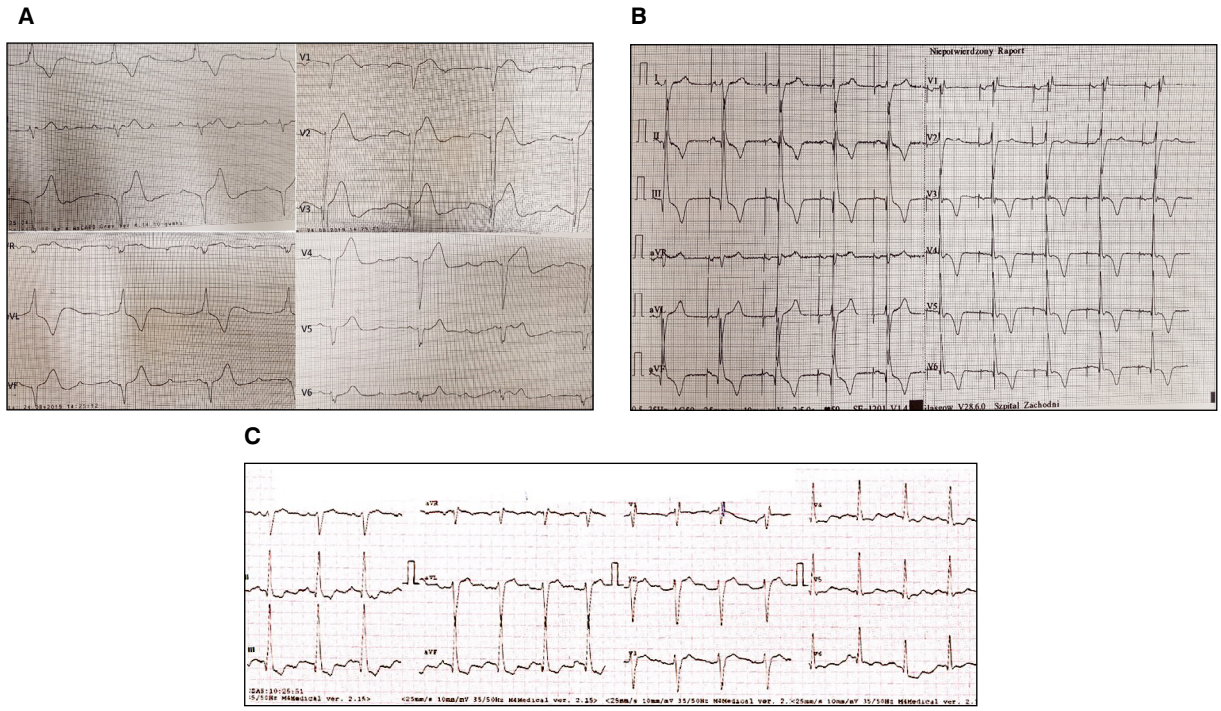


Figure 1. ECG recorded at 25 mm/sec. **A**. ECG on admission — third degree atrio-ventricular block, **B**. ECG after pacemaker implantation — dual chamber pacing, **C**. ECG during follow-up visit — normal sinus rhythm, left posterior fascicular block

roxime and penicillin G may be an option. Usually, two weeks of antibiotic therapy is recommended, whereas a 4-week course is recommended for chronic manifestations of Lyme disease [3, 6]. Temporary pacing may be required in unstable patients, but generally awaiting attitude is preferred. It is advisable to avoid temporary stimulation and if it is already used, it should be as short as possible [4]. Implantation of a permanent pacemaker is only exceptionally necessary [5]. Some centres use an option of applying modified transvenous temporary-permanent pacing, which is safer than temporary pacing, allows the patient to go home, and is relatively easy to remove after a few weeks. This method however it is not popular [7].

The early stage of borreliosis is evidenced by the rise in IgG titer and/or the presence of IgM [3]. There is a two-step approach in serological diagnosis, which is an initial screening test (ELISA), followed by a Western Blot carried out for reactive and equivocal ELISA samples [2, 3]. Due to delayed immune response, in the early stages of the disease serologic results may be false negative even in 50% of patients (an early diagnostic gap). Therefore negative serological tests cannot rule out the disease and in the case of clinical suspicion of LD the ELISA should be repeated, usually after 4 weeks [2]. In the late stages of Lyme disease, IgG levels are always elevated and their absence excludes the disease [2].

Diagnosis of Lyme carditis should be based primarily on the clinical presentation and an assessment of tick-exposure risk [2]. Therefore in the case of unexplained A-V conduction disturbances especially in young men, empirical antibiotic treatment is recommended [6]. The disease is then confirmed by positive Borrelia serology. There are attempts to make a general algorithm for diagnosis of LC and the Suspicious Index in Lyme Carditis score (SILC) is a novel risk score, that estimates the probability of LC in patients with A-V block [5, 8].

Case report

A 48-year-old man, not yet treated for any reason, was admitted to the hospital after multiple cardiac arrest episodes in the course of recurrent severe bradyarrhythmia. The patient lost consciousness and stopped breathing without any preceding symptoms. Cardiopulmonary resuscitation was undertaken by family members, then continued by an ambulance team. In ECG monitoring third-degree A-V block with escape rhythm 30/min with wide QRS complexes was found (Fig. 1A). After atropine administration, the third degree A-V block turned into a hemodynamically stable second degree A-V block and the patient regained consciousness. On the way to the hospital, however, there were many recurrent episodes of advanced A-V

Table 1. Two-steps serological diagnosis of Lyme disease: positive result of ELISA test (IgG) confirmed by Western Blot analysis (IgG against VisE and p41)

Screening test — ELISA		**Norms**	**Our patient**	**Comments**
Detects antibodies IgG and IgM against *B. burgdorferi s.l.*	IgM level in serum (RU/ml)	< 16 – negative result≥ 16R to < 22 – equivocal result ≥ 22 – positive result	3,57	The first step of diagnostics. High sensitivity of the test, which increases the risk of false-positive results (cross-reacting antibodies)
	IgG level in serum (RU/ml)	< 16 – negative result≥ 16R to < 22 – equivocal result ≥ 22 – positive result	46	
Verification test — Western Blot		**Proteins**	**Our patient**	**Comments**
Detects antibodies IgG and IgM against a wide range of proteins specific for *B. burgdorferi s.l.*	Commonly detectedproteins	p83	-	The second step of diagnostics. High specificity, performed to confirm infection in cases of positive or equivocal ELISA test
		Variable major protein-like sequence, expressed (VisE)	+ (IgG)	
		p58	-	
		Flagellin (p41)	+ (IgG)	
		Outer surface protein C (OspC)	-	
		Decorin Binding Protein A (DpbA)	-	

Table 2. Atrial (A) and ventricular (V) pacing percentage during pacemaker control

Time of the pacemaker control	**Atrial (A) and ventricular (V) pacing percentage (%)**
Discharge from hospital	A 7, V 100
One month follow-up	A 15, V 13
Three-month follow-up	A 16, V 0
One year follow-up	A 20, V 4

block with multiple cardiac arrests. The patient was administered further doses of atropine and received external pacing. Finally, he was put into a pharmacological coma, intubated and artificially ventilated. In the hospital transvenous temporary pacing was established. The physical examination and echocardiography did not reveal any relevant abnormalities. CT pulmonary angiogram, coronary angiography and head CT scan were performed, respectively ruling out pulmonary embolism, acute coronary syndrome and central nervous system disorders. Laboratory tests showed increased C-reactive protein concentration, there were no other abnormalities. Blood culture was collected and empirical intravenous antibiotic therapy with ceftriaxone, ciprofloxacin and metronidazole was started (standard initial combination used at the authors' institution due to the patient's poor general condition including artificial ventilation). The patient was kept in a pharmacological coma and artificially ventilated for two days. Then he was woken and extubated, however, he was still completely dependent on endocavitary pacing. For the next few days, he presented agitation and confusion, which was probably associated with multiple cardiac arrests and hypoxia to the central nervous system.

While taking a detailed medical history from the patient's wife, she could recall that he had been exposed to multiple tick bites about a month ago and 2 weeks ago she observed erythema on the skin of his thigh, the trace of which was still present at close examination. The serological diagnostics for LD was ordered. After 3 days (5th day of hospitalization) positive results were received - the level of specific IgG but not IgM was elevated. The results were confirmed in Western Blot analysis (Tab. 1). In subsequent serological tests, that were repeated after a week, IgM was again negative but increasing IgG titers were observed. Finally, LD with heart involvement was recognized so intravenous ceftriaxone therapy (2g iv once daily) was continued for 2 weeks. As blood cultures appeared to be negative, two other antibiotics were discontinued.

Despite several days of ceftriaxone therapy, the patient was completely dependent on endocavitary pacing. Finally, for suspicion of permanent damage to the conductive system and the history of multiple cardiac arrest episodes, on the 10th day of hospitalization, a decision was made to implant a permanent pacemaker (Fig. 1B). The pacing percentage in atrial and ventricular channels at discharge (14th day of hospitalization and antibiotic therapy) was 7 and 100% respectively. In pacemaker follow-up after one and three months, gradual A-V block regression and resolution of the pacemaker's participation in A-V conduction were observed, however, in a one-year follow-up, ventricular pacing again became visible (Tab. 2). In ECG made during the follow-up visits, normal sinus rhythm with a left posterior fascicular block (LPFB) was present, it is not certain, however, whether it is a remnant of the disease or the patient had it before (Fig. 1C).

Discussion

Plenty of cases of patients with advanced A-V blocks were published, but in a few cases, the course of the disease was so dramatic as in the presented patient case [9, 10]. In the majority of cases, antibiotic therapy was the only method of treatment and there was no need for temporary pacing nor permanent pacemaker implantation. In a systematic review made by Besant G et al. high-degree A-V block resolved in 94.3% of cases, with a median time to resolution of 5 days (3–9). A permanent pacemaker was implanted in 12.5% of patients, but in half of them, A-V block resolved after a course of antibiotics, and the pacemaker was removed or no longer required [8]. In another review, permanent pacing was necessary for 4.4% of patients [9]. Therefore, because of a known good prognosis and resolution of conduction abnormalities in most cases, the decision to implant a permanent pacemaker was not easy and not obvious. The pros were: extremely severe symptoms on admission, lack of IgM (not really an early stage of the disease?) and the need for temporary pacing for 10 days despite proper treatment. The latter mentioned might indicate permanent A-V conduction damage and additionally was associated with the patient's impaired mobility due to the risk of electrode dislocation and possible drawbacks, including infectious complications and mechanical, like perforation of the myocardium. As on discharge (14th day of antibiotic therapy), the patient was still pacemaker dependent, the decision seemed right at first, however, during the next three months A-V conduction disturbances gradually resolved. As there are no general guidelines concerning this topic, a question came up, whether the performed management was optimal. Should the decision about pacemaker implantation be deferred? Also, another puzzling issue arose — should pacemaker removal be considered since A-V block resolved? Taking into account that the residual LPFB might be a remnant of LC — would it be fully safe to remove the pacemaker? Does LPFB increase the patient's future risk of A-V block recurrence? No such data are available, which made the decision more difficult. The solution came with a follow-up visit a year after pacemaker implantation when it turned out that despite pacemaker settings promoting the patient's ventricular beats (interval between an atrial paced or sensed event and the ventricular pacing pulse was about 350 ms), the ventricular pacing was again present. It was 4%, which seems a small percentage, but actually, it is enough to lead to sudden cardiac arrest.

Conclusions

The most common form of LC is A-V blocks, which usually disappear during the first few days of antibiotic therapy. In some cases, however, the A-V conduction disturbances are severe, they last longer and can be even the cause of sudden cardiac death. Persistence of A-V blocks despite antibiotic therapy for more than one week rather indicate permanent damage to the structures of the conducting system and may indicate the need for permanent pacing. As there are no guidelines concerning the timing for the pacemaker implantation, management of the most severe patients should be individual.

Acknowledgements: *None.*

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

References

1. Stanek G, Wormser G, Gray J, et al. Lyme borreliosis. The Lancet. 2012; 379(9814): 461–473, doi: 10.1016/s0140-6736(11)60103-7.
2. Scheffold N, Herkommer B, Kandolf R, et al. Lyme carditis--diagnosis, treatment and prognosis. Dtsch Arztebl Int. 2015; 112(12): 202–208, doi: 10.3238/arztebl.2015.0202, indexed in Pubmed: 25838022.
3. Stanek G, Strle F. Lyme borreliosis-from tick bite to diagnosis and treatment. FEMS Microbiol Rev. 2018; 42(3): 233–258, doi: 10.1093/femsre/fux047, indexed in Pubmed: 29893904.
4. Lelovas P, Dontas I, Bassiakou E, et al. Cardiac implications of Lyme disease, diagnosis and therapeutic approach. Int J Cardiol. 2008; 129(1): 15–21, doi: 10.1016/j.ijcard.2008.01.044, indexed in Pubmed: 18508142.
5. Yeung C, Baranchuk A. Diagnosis and Treatment of Lyme Carditis: JACC Review Topic of the Week. J Am Coll Cardiol. 2019; 73(6): 717–726, doi: 10.1016/j.jacc.2018.11.035, indexed in Pubmed: 30765038.
6. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43(9): 1089–1134, doi: 10.1086/508667, indexed in Pubmed: 17029130.
7. Wang C, Chacko S, Abdollah H, et al. Treating Lyme carditis high-degree AV block using a temporary-permanent pacemaker. Ann Noninvasive Electrocardiol. 2019; 24(3): e12599, doi: 10.1111/anec.12599, indexed in Pubmed: 30265432.
8. Besant G, Wan D, Yeung C, et al. Suspicious index in Lyme carditis: Systematic review and proposed new risk score. Clin Cardiol. 2018; 41(12): 1611–1616, doi: 10.1002/clc.23102, indexed in Pubmed: 30350436.
9. Forrester JD, Mead P. Third-degree heart block associated with lyme carditis: review of published cases. Clin Infect Dis. 2014; 59(7): 996–1000, doi: 10.1093/cid/ciu411, indexed in Pubmed: 24879781.
10. Kashou AH, Braiteh N, Kashou HE. Reversible atrioventricular block and the importance of close follow-up: Two cases of Lyme carditis. J Cardiol Cases. 2018; 17(5): 171–174, doi: 10.1016/j.jccase.2018.01.001, indexed in Pubmed: 30279884.

VIA MEDICA

LETTER TO THE EDITOR

Klaudiusz Nadolny[1,2], Jerzy Robert Ładny[3], Robert Gałązkowski[4], Łukasz Pach[1], Waldemar Kraska[5]

[1]Faculty of Medicine, the University of Technology in Katowice, Katowice, Poland
[2]Department of Emergency Medical Service, Strategic Planning University of Dabrowa Gornicza, Dabrowa Gornicza, Poland
[3]Department of Emergency Medicine, Medical University of Bialystok, Bialystok, Poland
[4]Department of Emergency Medical Service, Medical University of Warsaw, Warsaw, Poland
[5]Ministry of Health, Warsaw, Poland

The medical rescue system in Poland in the era of the SARS-CoV-2 pandemic

Key words: SARS-Cov-2, COVID-19, emergency medical team

To the Editor:

The SARS-CoV-2 pandemic was first identified in December 2019 in Wuhan, China. Since then, the virus has spread all over the world, including Poland [1, 2].

A very important aspect of the fight against coronavirus is the emergency medical system, which concerns pre-hospital care. As part of the State Medical Emergency System, in 2020 there were 1,585 medical rescue teams in Poland (73% were basic teams, without a doctor) and 21 air medical rescue teams.

In the period before the pandemic, emergency medical teams intervened approximately 3.4 million times each year. The most common life-threatening conditions are sudden cardiac arrest, chest pain, shortness of breath, injuries, traffic accidents, suspected stroke. The period of the ongoing pandemic changed the functioning of the emergency medical system.

Retrospective analysis of departure order cards and medical rescue cards from 15/03 to 15/05 in 2018–2020, showed a large decrease not only in interventions but also in individual disease symptoms. The data was prepare d thanks to the Command Support System of the State Medical Rescue with the participation of the Ministry of Health. In 2018, 550,815 interventions of medical rescue teams were recorded, in 2019 – 527,837, but already in 2020, during the SARS-CoV-2 pandemic, already 400,878 ($p < 0.001$). This is a drop in quantity by more than 20%. Due to the reduced traffic on the roads, there was a decrease in traffic accidents by almost 50% and injuries by over 30%, and reasons for calling "fainting" by over 40%. The call for chest pain decreased by more than 15%, for breathing disorders (dyspnoea) by almost 20%. Only the call to suspect a stroke in the analysed period is at a similar level. The interventions for sudden cardiac arrest increased (by 5–10%) [3].

We read the article by Gąsior et al. [4] with great interest. Where the analysis occurred of the medical rescue system data concerned departure order cards and emergency medical cards in the period from 11/03 to 26/04 in the years 2019–2020. In the analysed voivodeships, by April 26, 2020, 2,599 infections were found – the most in the Śląskie Voivodeship – 1,867 people, in the Opolskie and Podlaskie voivodeships 363 and 369 infections, respectively. In all voivodeships, a decrease in the number of calls of emergency medical teams due to chest pain was observed, by an average of 8.3%. The number of diagnoses of a heart attack made by the head of the emergency medical team decreased by 22.3%. The number of hospitalizations due to myocardial infarction decreased by an average of 43.6%.

The occurrence of the common causes of intervention by emergency medical teams, e.g., chest pain, injuries, fainting, suspected myocardial infarction significantly decreases in the COVID-19 era and similar trends were observed in Poland and other countries [5, 6].

Medical Research Journal 2021; Volume 6, Number 1, 75–76, DOI: 10.5603/MRJ.a2021.0011, Copyright © 2021 Via Medica, ISSN 2451-2591, e-ISSN 2451-4101

Corresponding author: Klaudiusz Nadolny, Faculty of Medicine, Katowice School of Technology, Katowice, Poland, Rolna 43 Str., 40-555 Katowice, e-mail: knadolny@wpr.pl

Conflict of interest: *None declared.*

References

1. Nowak B, Szymański P, Pańkowski I, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med. 2020; 130(5): 407–411, doi: 10.20452/pamw.15361, indexed in Pubmed: 32420710.
2. Wierzbik-Strońska M, Nadolny K, Grabarek B, et al. Characteristics of the intervention of emergency medical teams in the southern part of Poland in 12-month observation. Wiad Lek. 2020; 73(8): 1632–1636, doi: 10.36740/wlek202008108.
3. Kucap M, Nadolny K, Ładny JR, et al. Interventions of emergency medical teams in Poland during the SARS-CoV-2 pandemic. Kardiol Pol. 2021; 79(1): 72–75, doi: 10.33963/KP.15632, indexed in Pubmed: 33021351.
4. Gąsior M, Gierlotka M, Tycińska A, et al. Effects of the coronavirus disease 2019 pandemic on the number of hospitalizations for myocardial infarction: regional differences. Population analysis of 7 million people. Kardiol Pol. 2020; 78(10): 1039–1042, doi: 10.33963/KP.15559, indexed in Pubmed: 32820878.
5. Nadolny K, Zyśko D, Obremska M, et al. Analysis of out-of-hospital cardiac arrest in Poland in a 1-year period: data from the POL-OHCA registry. Kardiol Pol. 2020; 78: 404–411.
6. De Rosa S, Spaccarotella C, Basso C, et al. Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J. 2020; 41(22): 2083–2088, doi: 10.1093/eurheartj/ehaa409, indexed in Pubmed: 32412631.

VIA MEDICA

LETTER TO THE EDITOR

Monika Zawadka-Kunikowska[1], Paweł Zalewski[1], Julia L. Newton[2]

[1]Department of Hygiene, Epidemiology, Ergonomy and Postgraduate Education, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Torun, Poland
[2]Population Health Science Institute, The Medical School, Newcastle University, Framlington Place, United Kingdom

The similarities between Long-haul COVID-19 and myalgic encephalomyelitis/ /chronic fatigue syndrome (ME/CFS)

Key words: ME/CFS, Long-haul COVID-19, fatigue

To the Editor:

A large number of research studies are currently collecting data about the whole range of short- and long-term health effects associated with SARS--CoV-2 infection. Long COVID-19, post-COVID-19 also known as Long-haul COVID-19 is the current name being given to the long-term sequelae (persistent symptoms experienced longer than 6 weeks) of SARS-CoV-2 infection. An estimated 10% of patients with COVID develop Long-haul COVID-19 symptoms [1]. Initial reports suggest that post viral fatigue (PVF) and Post viral fatigue syndrome (PVFS) are the most common long term issues in individuals infected with SARS-CoV-2. The severity and duration of the acute viral infection are strong risk factors for the development of fatigue syndromes. According to an Australian research group, approximately 12% of 253 subjects developed a Post Viral Syndrome that involved fatigue, cognitive dysfunction, mood disturbance and musculoskeletal pain [2].

Postinfectious syndromes including those seen with persistent symptoms after COVID-19, often share a common symptom phenotype, that is either self-limiting or has features that are very similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [1, 3]. Recently, there have also been reports about a high frequency of patient-reported Long-haul-COVID-19 symptoms that as well as fatigue include cognitive difficulties (problems with short term/working memory, concentration, information processing), pain, orthostatic intolerance (problems in remaining upright, feeling dizzy), anxiety/depression, sleep and autonomic disturbances [4]. One symptom that is considered to be unique to ME/CFS is post-exertional malaise (PEM). PEM can be described as delayed and significant exacerbation of ME/CFS symptoms that always follow physical and cognitive activity [1].

Although ME/CFS and Long-haul COVID-19 are medically distinct, they share a common pathological process including viral infection, altered mitochondrial dynamics with sequent oxidative stress, pro-inflammatory state, cytokine production, and cell death [3]. Acute Epstein-Barr virus (EBV) infection is an important virus trigger of ME/CFS. Some researchers speculate that SARS-CoV-2 could replace the EBV as being the most frequent precipitating event for ME/CFS or Long-haul COVID-19. Considering the overlapping of symptoms, ME/CFS and Long-haul COVID-19 should be better characterized as post active phase of infection syndromes (PAPIS) [1]. Furthermore, the opportunities to learn about pathophysiology and treatments from the study of these commonalities and differences in each disease should be recognised.

PVFS may also result from immune system overreaction associated with ongoing production of increased cytokine levels, especially interleukins 6 and 10. These cytokines are also thought to play a key role in immune dysregulation and are frequently reported as abnormal in many cases of ME/CFS. In patients with Longhaul-19 symptoms lasting for more than 3 months with a functional impairment that prevents a return to everyday activities (education, employment) a diagnosis of ME/CFS should be considered. [2–3].

Medical Research Journal 2021; Volume 6, Number 1, 77–78, DOI: DOI: 10.5603/MRJ.a2021.0013, Copyright © 2021 Via Medica, ISSN 2451-2591, e-ISSN 2451-4101

Corresponding author: Paweł Zalewski, Department of Hygiene, Epidemiology, Ergonomy and Postgraduate Education, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus, Copernicus University in Torun, Poland, e-mail: p.zalewski@cm.umk.pl

Patient evidence also indicates that a good initial approach to the management of PVS reduces the probability of this turning into ME/CFS. The standard approach to the management of any form of significant post viral fatigue involves convalescence and a gradual return to normal daily activities. A recent study using an MRI scan showed cardiac inflammatory involvement in both hospitalised and non-hospitalised subgroups. Thus, proper evaluation of cardiac and respiratory function is needed [2]

This is an important time for those currently with, or at risk of postinfectious syndromes which includes some with ME/CFS. Exploration of the causation and effective treatment of such syndromes will improve the understanding and treatment regardless of the triggering illness. Novel research into COVID-19 may lead to a much better understanding of the role of the immune response and why some people develop post viral syndromes and ME/CFS [1, 4].

References

1. Friedman KJ, Murovska M, Pheby DFH, et al. Our Evolving Understanding of ME/CFS. Medicina (Kaunas). 2021; 57(3), doi: 10.3390/medicina57030200, indexed in Pubmed: 33652622.
2. Shepherd C. Post COVID-19 Fatigue, Post/Long Covid-19 Syndromes and Post-Covid ME/CFS. www.meassociation.org.uk (September 2020).
3. Gaber T. Assessment and management of post COVID fatigue. Progress in Neurology and Psychiatry. 2021; 25(1): 36–39, doi: 10.1002/pnp.698.
4. Aucott JN, Rebman AW. Long-haul COVID: heed the lessons from other infection-triggered illnesses. Lancet. 2021; 397(10278): 967–968, doi: 10.1016/S0140-6736(21)00446-3, indexed in Pubmed: 33684352.