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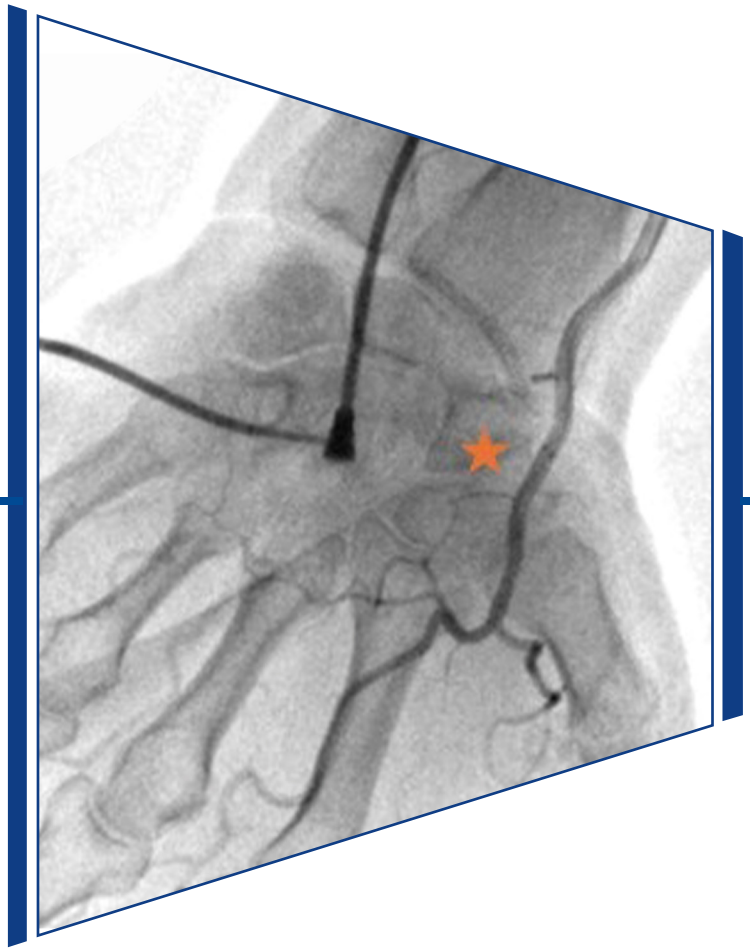

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Photo on the cover of the issue by Łukasz Koziński et al. (page 62)

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INVITED EDITORIAL

Avian influenza: the looming threat of Disease X and lessons from Poland and Europe

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Abstract

The ongoing outbreak of highly pathogenic avian influenza such as A/H5N1 virus, with its continued evolution and spread to various mammalian species, raises significant concerns about its potential to cause a human pandemic. This editorial examines the recent spillover events to mammals, the economic impact on the poultry industry and the importance of preparedness and preventive measures. The situation in the USA (widespread outbreaks in cows as well as in dairy farm workers) and in Europe (infections in cats and fur animals) highlights the urgency of implementing effective surveillance, biosecurity, vaccination and communication strategies. Particularly, we focus on the lessons learnt (and also those not learnt) from Poland and the rest of Europe in managing potentially being zoonotic outbreaks of unknown origin. Personal experience from these events, though potentially reflecting the subjective views of the authors, highlight the importance of regional preparedness and rapid response to mitigate the risks posed by avian influenza and other emerging infectious diseases. A One Health approach, integrating the animal, human and environmental health sectors with socioeconomic constraints, is crucial for mitigating the risks and preventing a potential global health crisis.

Keywords: avian influenza · sociology of medicine · Disease X · preparedness · One Health

Citation

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Introduction

Avian influenza, colloquially known as bird flu, is an infectious disease caused by type A influenza viruses (AIV) that occurs naturally in wild birds, mainly waterfowl. Classification of influenza viruses is based on the antigenic properties of their surface proteins; hemagglutinin (H) and neuraminidase (N). It is a disease with high mutation rates and the potential for zoonotic transmission [1]. Avian influenza challenges both the veterinary and medical communities. Recent outbreaks in various locations around the world revealed the urgent need for comprehensive mitigation strategies, particularly as concern rises over the emergence of a potential Disease X (a term reserved for an unknown pathogen that has the ability to cause a large-scale epidemic). AIV is shortlisted for high priority potential Pathogen X particularly for Europe [2]. Of particular concern are cases of virus spillover to mammals, i.e. its transfer from birds to other animal species, which increases the risk of mutation and adaptation of the virus to humans. An example of such a phenomenon in the last 2 years is an epizootic of H5N1 virus in cows and among other mammals in the United States of America (USA) in 2024 and cats in Poland or in fur animals in Finland in 2023 [3-5].

Poland, located in central Europe, has seen numerous outbreaks of avian influenza in years 2020-2024, providing crucial insights about disease prevention and control [6]. Poland's geographical location and its extensive poultry industry make it an essential area for studying the spread and management of avian influenza across Europe [7].

In this editorial we aimed to discuss the various threats posed by avian influenza, particulary in the context of a potential Disease X [8]. By analyzing Poland's experiences and the wider European perspective, we aim to identify strategies and policy recommendations that could be implemented on European scale, covering the biological, ecological and socioeconomic aspects of avian inflIuenza. We highlight the importance of preparedness, quick response and international cooperation to prevent future pandemics of zoonotic origin [9]. Our discussion includes scientific findings in virology, epidemiology and veterinary science, as well as case studies from European countries, including Poland. We also want to signal what went wrong [10]. By synthesizing these insights, we hope to contribute to a more resilient and informed approach in managing the ever-imminent risk of avian influenza and other emerging infectious diseases.

History of avian influenza

The H1N1 influenza pandemic of 1918-1920 (incorrectly named "Spanish flu") which caused the death of estimated 50-100 million people worldwide was an avian-like H1N1 virus [11]. The so-called Hongkong H3N2 pandemic virus was a reassortment virus (i.e. the exchange of genomes between different viruses living in the same host) of a seasonal human influenza virus and a low pathogenic avian influenza A virus [12-13]. It caused millions of infections in Europe between 1969-1971, which froze the economy and was one of the triggers of a reduced quality of life. In terms of registered cases, it was the largest epidemic in modern Polish history, far more so than the COVID-19 in 2020-2024. At the peak of the H3N2 epidemic (December 1970), almost half of the staff in Poland's factories were either on sick leave or on strike. The avian strain H5N1, the lead topic of this editorial, killed at least 90 people in 2003/2004, mostly in South East Asia [14]. Although experience to date shows that human-to-human transmission is generally low, the mortality rate can be as high as 50% [15]. The 2009/2010 H1N1 pandemic was caused by a unique combination of swine, avian and human influenza. Other than HIV and coronaviruses, all major pandemics in modern history were caused by avian influenza [16]. It is worth noting that since 2022/2023 the seasonal human influenza rates have returned to pre-COVID-pandemic level in the European Union (EU) [17].

Virology and epidemiology

Due to the close contact and proximity of humans and animals throughout our shared history, many pathogenic microorganisms have evolved to effectively infect both types of hosts. These are zoonoses and reverse zoonoses (crossing from humans to the animal population) [18]. In the case of COVID-19, there is evidence that it might be a zoonotic disease from the start of the pandemic and later it evolved to a reverse zoonotic disease as well [19-20]. It led to disastrous implications for selected livestock populations. In particular, it caused the slaughtering of minks in 2020/2021 following the transmission of the SARS-CoV-2 virus from humans to minks, also in Poland [21]. In addition to the significant impairments caused by zoonotic diseases affecting livestock (e.g. the reduced access to food of animal origin), a region or country may experience a reduction in its ability to export or trade agricultural and food products during an outbreak/epizootic. Global livestock production and agriculture are heavily dependent on biosecurity measures along the production-consumption chain. We should also note the challenges to biosecurity requirements in the context of the current European Union's Green Deal strategy of "from the farm to fork" [22]. Poultry producers are the first to experience the resulting restrictions (e.g. in antibiotic administration to livestock), while biosecurity (also against AIV) is promoted [23].

General virology of avian influenza

AIV, like all viruses (particularly RNA), are constantly mutating [24]. The farm environment allowed the reassortment of the H5 and H8 subtypes to occur. Thus, the viruses evolved from low pathogenic (LPAI) to lethal to domestic poultry (highly pathogenic, HPAI) [25]. If the virus mutates to a form that is easily transmitted from birds to humans (a so-called spillover), a serious public health crisis could emerge. In 2023 thousands of outbreaks have been reported in poultry, wild birds and, most alarmingly, in mammals [26]. The situation in the USA during the spring/summer of 2024 was unprecedented: an extremely large outbreak in mammals (mainly cows) and dozen confirmed cases in humans (with contact with animals) [27-28]. Upon submission (August 6th 2024), there were 1838 registered human cases of H5N1 since the beginning of this linkage around 1993 with 13 notifications from the current outbreak in the USA [29]. Probably more human cases are unreported. Besides, non-infectious AIV fragments appeared in dairy products or in sewage, also in the areas of USA without industrial dairy farms [30].

Genetic changes and adaptations of H5N1 in 2022-2024

The ongoing global outbreak of H5Nx virus, originating from the goose/Guangdong lineage, has persisted for over 25 years. It has diversified into 8 distinct groups (2.3.4.4a-2.3.4.4h) with 3 primary neuraminidase subtypes: N1, N8, and N6 [31]. Notably, the H5N1 subtype within this lineage (clade 2.3.4.4b) has been responsible for the last decade of global outbreaks. This strain has undergone rapid and significant genetic changes through reassortment of internal genes. In a short timeframe, it has outcompeted other avian influenza strains and is now prevalent in wild migratory bird populations across Asia (its primary source), Europe, Africa and the Americas [32]. Throughout this time, the virus has continuously evolved, resulting in the emergence of several distinct genetic clades of the H5 hemagglutinin gene. Variants of the H5N1 group have been monitored for several years and spread on all continents [31]. Mammals in Europe (2023) and the USA (2024) were infected with a reassortant virus and continuation of the lineage 2.3.4.4b [33]. There are several viral genes to be analyzed phylogenetically: polymerase-binding protein 1, 2 (PB1, PB2) matrix protein (MP), non-structural protein (NS), acidic protein (PA), nucleocapsid protein (NP). Changes in the NP part of AIV were linked with previous pandemics in humans, thus they are the most interesting in terms of zoonotic potential [34]. Mutations in PB2, specifically E627K, are genetic indicators of the virus ability to infect mammals [35]. All the viruses from cats and most other European mammals exhibit this mutation [36]. The virus found in the white stork in Poland in 2023 exhibited some of these characteristic mutations in NP and PB2 [35].

Thus, based on the available material, certain sets of SNPs (single nucleotide polymorphisms), previously marked as related to circulation in mammals, can persist in European bird populations, including both wild and domestic. However, these mutations do not tend to infect mammals unless they reassort with strains imported from Africa by the migrating bird population, which might explain the seasonal dynamics of the outbreaks. Phylodynamic of ongoing outbreak in cows in the USA suggest a different mechanism and Pan-American origin [37].

Social determinants of recent avian influenza outbreaks

Between April 1st (first confirmed human case in a dairy worker) and and April 21st 2024 (detection of non-infectious parts of AIV RNA in milk) the problem of avian influenza has caught the attention of the general public, which is usually not interested in non-human diseases (Figure 1) [38]. These dates started a new era in avian influenza. Although infections in cattle in March 2024 were of interest in the professional community only, the milk contamination and partially human cases among dairy farm workers gained greater recognition.

The southern hemisphere's influenza-like illness (ILI) season began in May 2024, with a significant impact on pediatric patients [39]. The case of H5N1 in a child in Australia attracted the most attention and generated considerable traditional media coverage and social media discourse (peak around May 22nd 2024, Figure 1) [40-41]. This case demonstrates that media and public interest depend not only on the epidemiological significance of an event, but also on its emotional and socioeconomic context [42].

Since peaking in 2021, cases in wild birds and poultry in the EU/European Economic Area were on decline until the beginning of the summer in 2024 [33]. However, viruses found new host species during the spillover in spring/summer 2023. Avian influenza used to have seasonal patterns (e.g. in Poland peaks around early spring, late summer), but these patterns are less and less visible since 2022 [26]. To cope with highly pathogenic avian influenza, the poultry industry and wild bird conservation programs must be transformed in line with an integrated One Health approach that recognizes the interconnectedness of human, animal and environmental health in addressing global health challenges [1].

Consequences of avian influenza

Avian influenza is not only a concern for epidemiologists, but also a major economic problem because if the virus is detected, all the birds in that particular flock have to be killed.

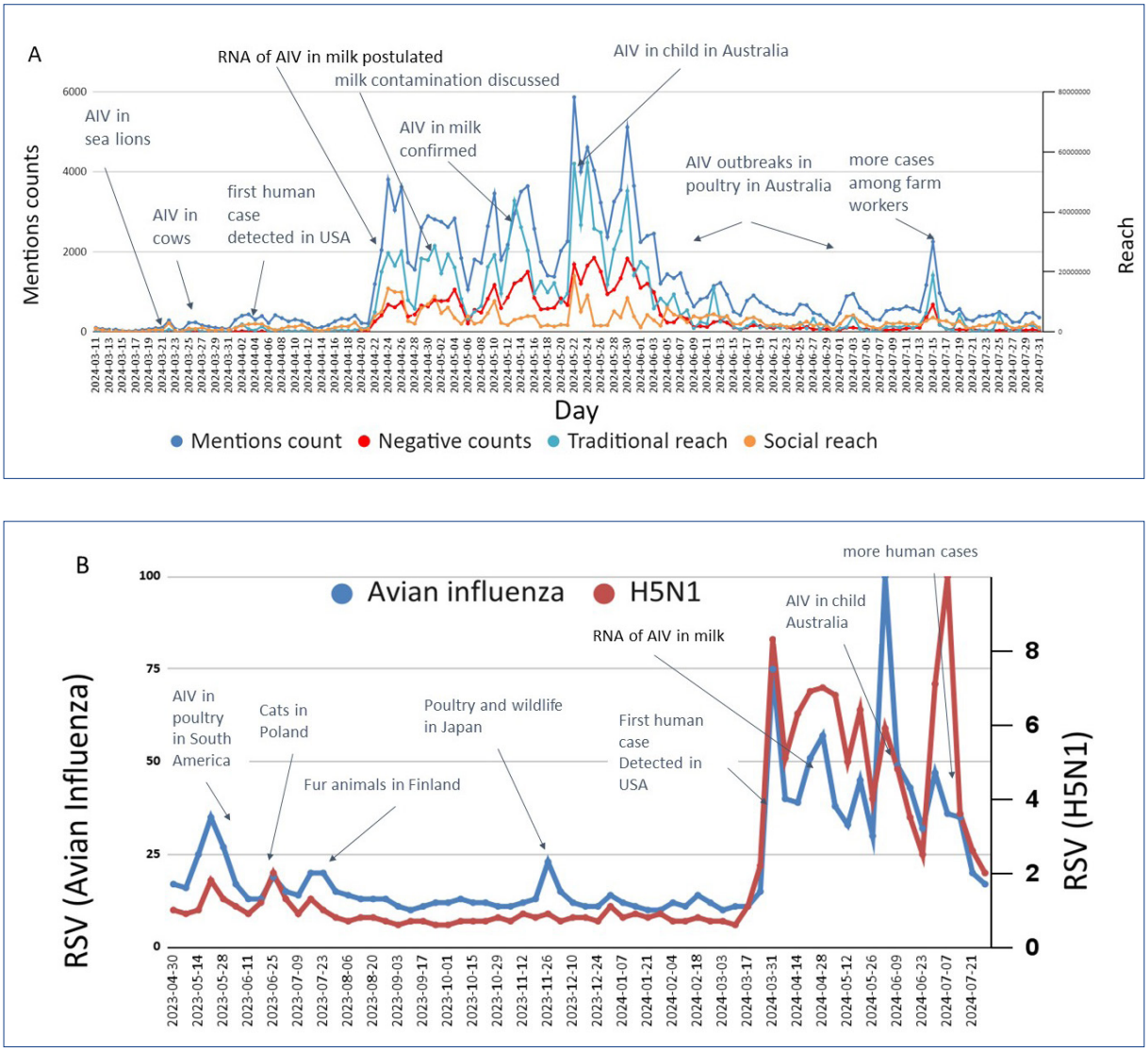

Figure 1. A – Discourse (information supply) volume with sentiment: the emotional attitude expressed in a text (left axis) and reach (right axis) for given keywords (*avian influenza* and *bird flu)* in English during March-July 2024 (collected with Brand 2024); B – *Avian influenza* (left axis) and *A/H5N1* (right axis) in Google Trends (information demand) worldwide 5/2023-07/2024

The virus has infected wild birds in large areas of Europe (mainly in the West and the North), causing mass mortality. H5N1 is suspected of affecting biodiversity by causing mass mortality events in some mammals, such as the reported sudden deaths of over 20000 South American sea lions [43]. During 2020-2023 hundreds of millions of poultry were culled in Poland, France and Russia alone. It is also an economic diplomacy challenge to negotiate with countries that import European poultry meat due to concerns about AIV infection. It is noteworthy that Poland is the largest producer of poultry meat in the EU and the third largest exporter in the world [7].

Financial and social costs of avian influenza

In 2021 alone, the direct costs of combating avian influenza in Poland exceeded 100 million EUR (mainly due to the euthanasia of millions of birds) and if we add the indirect costs incurred by the farmers (problems with sales and biosecurity), it will easily exceed 250 million EUR [44]. The periods without any bird flu outbreaks in Poland or France are brief and in accordance with the regulations of many countries around the world, the occurrence of at least one case is associated with an embargo on the import of poultry [45].

Due to the fact that industrial farming is a breeding ground for new AIV variants, there are recommendations to

limit the global poultry population, including reducing intensive production in countries such as Poland [46-47]. However, countries with less developed poultry production, e.g. most of the Global South, should increase production [48]. This is due to the fact that poultry and eggs are perceived as quality protein sources with good biomass conversion, relatively low CO_2 emissions and lack of religious taboos. In contrast, countries with intensive poultry production, e.g. the USA, Poland or France, should drastically reduce production. On the other hand, climate change is making it more difficult to farm animals in subtropical climates (Africa, Central America, Asia and Southern Europe) due to insufficient access to water and heat waves, thus moving production to the colder zones. It is an opportunity for the development of the industry in Poland and the rest of Central/Northen Europe, but at the same time it poses threats [48]. Climate change also affects the migration corridors of birds, e.g. the southern coast of the Baltic Sea has become a new hot-spot, where contact between birds may occur and virus variants may spread over long distances [49-50].

High concentration of the poultry industry (e.g. in the Żuromin district, Central Poland) is a biosecurity problem (e.g. due to a multi-point outbreak in this area > 10 million birds were culled in a dozen days) [6]. Thus, deconcentrating these massive production centers in Poland and in France is worth considering. Biosecurity measures are very important, however there are also plenty of vaccines against HPAI H5 strains for poultry in use around the world [32, 51]. One of the reasons why vaccination is not so widespread is because of trade restrictions. The use of live vaccines causes vaccine strains to circulate in the population, which is a problem for trading with avian influenza-free countries (concerns about importing a vaccine strain). For example, France introduced mass vaccination of poultry in late 2023 because it had previously been blocked by trade restrictions [52]. Avian influenza vaccines (for H5N1) for humans are on the market, their production can probably be scaled up, but they have never been used in clinical practice until 2024 [53].

In 2023, there was a significant shortage of eggs in Russia, which led to price increases and widespread concern of availability among consumers and policymakers. The situation was also seen in the Kaliningrad Oblast (province) bordering Poland [54]. Although the export of eggs was officially forbidden, the demand provoked smuggling [55]. Among the constellation of factors related to ongoing Russia-Ukraine War (such as sanctions), avian outbreaks reduced the supply of eggs. In a single outbreak in Bashkiria Oblast in summer 2023, millions of laying hens were euthanized, and production in this area returned to normal conditions in 2024 [56]. The avian influenza-driven shortage of eggs occurred also in Australia in July 2024 (Figure 1) [57].

Case study: H5N1 in cats and fur animals in Europe

In Finland, the H5N1 virus outbreak at fur animal farms happened in the summer and autumn 2023. This time the virus most likely originated from wild birds, particularly gulls, and spread to farmed fur animals like foxes and minks [5]. Control measures included culling the infected animals, surveillance of the environment and wildlife, improving biosecurity, monitoring human exposure and securing vaccines for animal farmers. There were no problems with financing testing and monitoring, unlike in the case of the outbreak among cats in Poland. While no human infections were detected, the outbreak in Finland raises concerns about potential virus adaptation and transmission risks for future virus selection processes [48].

The H5N1 outbreak in cats in Poland did not have the same direct source as the Finnish outbreak and it resulted in circa 40 confirmed cases and hundreds of suspected dead cats. The exact case definition did not exist before, therefore the World Organization of Animal Health (WOAH) and other institutions (e.g. the Polish Veterinary Inspection) may provide slightly different numbers. The response of the authorities demonstrated effective regional control measures (primarily in Gdańsk), but revealed gaps in the national and international preparedness and communication [4]. Despite their limited financial capability, the local authorities quickly responded to contain the outbreak, while the lack of established protocols and coordination between agencies for human and animal health caused confusion and delays. The situation was further complicated by an infodemic from both the cat owners and the poultry industry, with conflicting information hindering effective control. The most important lesson learnt from the outbreak in Poland was the lack of effective collaboration between institutions. There were tensions between:

1) the regional and national inspections (compare with other One Health disasters, e.g. the 2022 massive fishkill in the Oder River caused by toxic algae blooms);

2) Departments of the Ministries responsible for health, agriculture and environmental protection (e.g. in Finland veterinary inspectors collected samples from wildlife, whereas in Poland this was not possible in case of certain species (e.g. white stork), due to the lack of permissions from environmental agencies);

3) citizens, governmental and scientific entities [4, 58].

In 2023/2024 more cases of AIV in Europe were detected among mammals such as dogs in Poland and Italy, multiple fur animals outside of Finland and cats outside of Poland among others [33, 59]. Course of the the avian influenza disease varies between species: it is similar to common cold in dairy cattle, while most often fatal in cats [36]. One and public health authorities both in Poland and the USA experienced similar challenges. For instance, a significant proportion of humans

in contacts refused to stay under sanitary surveillance or get tested [60]. Similar mis/dis-information topics (e.g. conspiracy theories about "the next planned pandemic") were circulating [4]. Although none of European mammal infections were proved to be transmitted from mammal to mammal, this was confirmed in the USA [37].

Preventive measures and preparedness

In the face of potential threats like avian influenza, we could implement the following key measures:

1) epidemiological monitoring;

2) counteracting processes that cause vulnerability;

3) developing new medical technology and promoting their use;

4) preparation of health infrastructure and coordination of service activities [61].

It is important to combine theoretical understanding with practical application as well as with the experience from COVID-19 and to utilize advanced technologies to create comprehensive plans for preventing and managing zoonotic diseases in our region (Baltic Sea) and across Europe [62-63] (Table 1). In humans, infections are typically related to direct contact with contaminated environments or animals that are either dead, sick or healthy-looking but infected (this is the case for dairy farm workers) [28]. Human infections of currently circulating H5N1 strains result in an asymptomatic or mild disease, causing symptoms ranging from fever, conjunctivitis and cough to ocular discharge. It can also cause atypical symptoms e.g. gastroenteritis, which makes it difficult to differentiate from another ILI [64]. In the late spring and summer between ILI seasons, an increase in the number of patients with respiratory symptoms (COVID-19 excluded) may need special attention. Moreover, a new spillover may result in a different symptom onset, thus close collaboration between family doctors and veterinary/sanitary inspection (mainly in rural areas) is needed to not overlook such events.

Table 1. Comprehensive preparedness approach to counteract potential avian influenza threats

Area of focus	Key actions	Relevant authorities/ entities
Surveillance and monitoring	Intensify monitoring of food supply chains, environment, farm animals and human-animal interactions using AI-supported systems, ensuring robust risk communication to stakeholders.	Sanitary and Veterinary Inspection (at the regional, national and international levels)
	Collaborate with international organizations (WHO, FAO, WOAH) for coordinated surveillance efforts to ensure early detection of potential threats and response. Ensure that all actions are supported by robust legal and regulatory frameworks.	public health authorities, international organisations
	Conduct targeted surveillance of wild birds during migration seasons (late summer and early spring) to detect early signs of avian influenza. Include equity considerations to ensure rural and remote areas are not disproportionately affected.	public health authorities, regional Veterinary Inspection
	Digitalise and integrate multiple registries to improve data sharing across health, agriculture and environmental agencies, ensuring data security and privacy. Highlighting the 2023 Legionella outbreak in Rzeszów (southern part of Poland) as an example of the consequences of poor information flow: agencies under 3 separate Ministries (of Health, Internal Affairs and Defence) performed separate investigations with no data sharing [65-66]. Monitor and evaluate these systems regularly.	Ministries responsible for health, agriculture, environment, internal affairs, defence
	Investigate atypical outbreaks with consideration of potential bio/agro-terrorism scenarios to ensure comprehensive threat assessment and response (due to the current geopolitical circumstances in Europe) [67].	military epidemiological entities, agencies responsible for health, agriculture, environment

AI – artificial intelligence; FAO – Food and Agriculture Organization of the United Nations; WHO – World Health Organization; WOAH – World Organisation for Animal Health

Table 1. Comprehensive preparedness approach to counteract potential avian influenza threats (continued)

Area of focus	Key actions	Relevant authorities/ entities
Surveillance and monitoring	Raise public awareness about the importance of reporting unusual incidents, particularly in relation to animal health and food safety, to enhance early warning systems. Communication strategies for topics related to companion animals to be prepared in advance (due to emotional bond between pets and their owners) [68].	public health authorities, communication specialists
	Apply stringent biosecurity principles to monitor and limit disease transmission within animal herds, focusing on preventive measures at the farm level [69].	veterinary authorities, farmers
	Regulate poultry production density and control imports (particularly from regions with lower veterinary controls) to maintain high health standards and prevent disease spread.	government administration, EU trade authorities
Crisis management and decentralisation	Decentralise decision-making to empower regional emergency management teams, enabling them to respond swiftly and effectively to local threats. Legal and regulatory frameworks should support these decentralised actions.	regional health and veterinary authorities, crisis management teams
	Provide ongoing training and capacity-building for regional emergency teams to ensure readiness for emerging threats. Build resilience against food disinformation and biological denialism [70-71].	regional emergency management authorities, training institutions
	Establish and maintain clear communication channels between regional and central authorities to facilitate coordinated responses to health emergencies, ensuring consistent risk communication.	regional and central health/ veterinary authorities
	Industry lobby groups (e.g. poultry producers) should not influence the governments in anti-health subjects as it happened during the 2024 farmers' protest in several European countries, which is in line with other lobbying efforts (e.g. the nicotine case) [72-73].	government administration, regional authorities
	Build regional resilience by coordinating activities at the sub-national level, recognizing the unique challenges of different regions, as seen in the effective responses in the Pomerania region of Poland.	regional health/veterinary authorities
	Ensure that the regional teams have access to adequate funding and resources to manage crises effectively, avoiding the over-reliance on central authorities. Monitor and evaluate the effectiveness of these strategies regularly.	national government administration, regional authorities
Public health and vaccination	Encourage poultry and animal farm workers to vaccinate against seasonal flu.	healthcare authorities, farmers, Regional Sanitary Inspection agency
	Provide timely access to tests and antivirals for farm workers displaying suspicious influenza-like symptoms, ensuring early treatment and containment.	healthcare providers, regional Sanitary Inspection

AI – artificial intelligence; FAO – Food and Agriculture Organization of the United Nations; WHO – World Health Organization; WOAH – World Organisation for Animal Health

Table 1. Comprehensive preparedness approach to counteract potential avian influenza threats (continued)

Area of focus	Key actions	Relevant authorities/ entities
Public health and vaccination	Support the rapid development and stockpiling of vaccines and antivirals based on the lessons learnt from the COVID-19 pandemic, ensuring preparedness for a more severe outbreak [16].	healthcare authorities, vaccine manufacturers
	Strengthen health systems to prepare for a potential pandemic that could pose a greater burden than COVID-19, with a focus on scalable response capabilities. Monitor and evaluate the effectiveness of these preparedness strategies regularly.	national health systems, pandemic preparedness committees
	Develop and implement logistics for equitable vaccine distribution, with ongoing monitoring of vaccine effectiveness, particularly in rural areas among animal farmers [53].	healthcare authorities, logistic and monitoring teams
	Conduct public health campaigns to increase vaccination uptake, with a focus on educating rural and remote communities about the benefits of vaccination. Incorporate equity considerations to ensure fair access to vaccines.	public health authorities, communication specialists
Biosecurity and food production	Implement robust biosecurity measures on farms to monitor and prevent the introduction and spread of diseases, with a focus on proactive risk management. Monitor and evaluate these biosecurity measures regularly.	veterinary authorities, biosecurity experts
	Invest in research and development to advance biosecurity practices, exploring new technologies and methods to enhance disease prevention and control [63]. Ensure that all research is supported by appropriate legal and regulatory frameworks.	government administration, research institutions
	Engage stakeholders (e.g. including farmers, industry representatives and environmental groups) in developing and implementing biosecurity measures that are practical and effective. Ensure equity considerations are embedded in the stakeholder engagement processes.	stakeholders (farmers, industry representatives, environmental groups), government administration
	Counteract the spread of misleading narratives about food safety ("food disinformation") by leveraging cutting-edge technologies (e.g. AI), while remaining vigilant against industry lobbying.	food safety authorities, communication experts, AI developers
Infodemic management	Establish dedicated infodemic management teams to manage the spread of misinformation and disinformation, while also addressing the broader challenges of managing the infodemic itself [74]. Ensure that these actions are supported by robust legal and regulatory frameworks.	WHO, public health authorities, infodemic managers, communication specialists
	Use social listening platforms to monitor public sentiment in real-time, integrating this data with epidemiological insights to enhance communication strategies [75].	public health communication teams, AI and social listening platforms
	Develop a comprehensive taxonomy to classify and track disinformation narratives, facilitating targeted responses to emerging threats. Ensure that all measures are equitable and consider the needs of underprivileged groups.	public health authorities, infodemic management teams

AI – artificial intelligence; FAO – Food and Agriculture Organization of the United Nations; WHO – World Health Organization; WOAH – World Organisation for Animal Health

Table 1. Comprehensive preparedness approach to counteract potential avian influenza threats (continued)

Area of focus	Key actions	Relevant authorities/ entities
Infodemic management	Proactively counter the infodemic in public health by using AI and machine learning technologies to enhance monitoring and response efforts. Incorporate equity considerations in the deployment of these technologies [76].	AI developers, public health authorities, infodemic management teams
	Collaborate with social media companies to manage and counteract misinformation, disinformation and infodemic effectively.	social media platforms, public health authorities
	Implement educational initiatives aimed at improving digital literacy, helping the public to better recognize and resist misinformation and disinformation. Ensure that these initiatives are accessible to all population groups.	ministry responsible for public education, public health authorities
	Develop and execute crisis communication plans that are responsive to the quickly-evolving misinformation, ensuring accurate information dissemination during health emergencies.	public health authorities, communication specialists

AI – artificial intelligence; FAO – Food and Agriculture Organization of the United Nations; WHO – World Health Organization; WOAH – World Organisation for Animal Health

Conclusions

The recent outbreaks of the AIV (mainly the H5N1 strain) have raised global concerns due to its spread to mammals and thus potential for human and possibly high mortality rates [77]. The economic impact has been substantial, with hundreds of millions of poultry culled yearly in Europe and trade restrictions imposed. The virus takes a much higher death toll in wildlife. Avian influenza is not just a biological condition of One Health [4, 78]. It is also a state of social con-

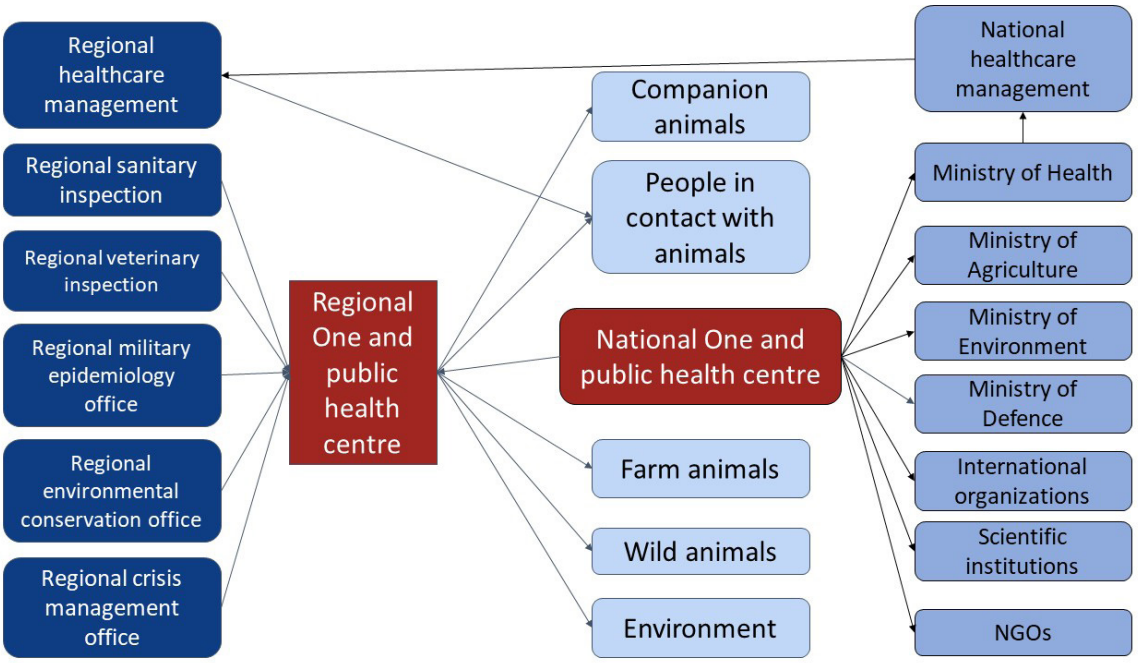

Figure 2. Structure of a surveillance/preparedness system (the initial phase of the EWRS – Early Warning and Response System [79]) which might be able to quickly react to Disease X threats such as avian influenza based on the experience with H5N1 in Europe in 2023 with major infectious agents; NGOs – non-governmental organisations

dition and a state of global order. It is a vulnerability that we have created (e.g. due to intensive poultry farming) and might have to face again.

Expecting the unexpected

The main problem revealed in 2023 in Europe in a totally new event was the lack of intersectoral coordination and collaboration, which suggested rethinking the practical implementation of the One Health concept in the EWRS (Early Warning and Response System) [80] (Figure 2). First of all, we need to strengthen local One and public health inspection agencies, which will need to take responsibility to detect abnormality in the very first weeks of an outbreak and later the responsibility may be shifted to national and international bodies [81-82]. The just culture of quality model emphasizes learning from errors and failures to improve preparedness, thus actual (not on paper only) coordination between regional One and public health inspection agencies is needed [83]. According to the Polish law, this responsibility belongs to the voivodeship (provincial) governor authority, but this was not the case in any of the recent One health crises: AIV in cats in Pomerania (Northern Poland, 2023), the Legionella outbreak in Southern Poland (2023) or the massive fishkill in the Oder river in Southern Poland (2022) [4, 66, 84]. The modern concept of risk reduction required: localized strategies (which we emphasize in this editorial the most), breakthrough endeavors, collective actions and cross-disciplinary coordination [85].

In the Pomerania case of avian influenza in cats, the investigation started on about June 15th 2023, when excess mortality was observed by veterinarians with the support of local cat owners (lay people) [86]. The virus most likely originated almost a month earlier in Southeastern Poland, but was not detected there on time [86]. Local part of the investigation lasted until the last days of June when cooperative work of regional inspections excluded mammal to mammal transmission (including to humans) as the main route. Most literature on preparedness focuses on national and international collaboration, while regional efforts are overlooked, and we have seen consequences of that in 2023 [87]. Thus, the so-called Situation Definition Phase (assessing, specifying and interpreting the current situation) requires regional expertise and capacities [88]. Organizing One Health crisis management teams at the regional level seems to be the best solution as it combines competence and sub-regional knowledge. In Poland (Pomerania) and the USA (Texas), regional health/veterinary authorities were able to identify the aetiology of unknown animal problems and manage them at an early stage with limited support from the national institutions. It is strongly recommended that cheaper new technologies, such as those based on artificial intelligence/machine learning, should be preferred to the traditional broad, expensive passive monitoring of different populations as advocated by some interest groups [63]. Most opinion articles and letters to the Editor simply emphasize the need for more AIV preparedness funding. We propose instead to use existing resources and skills and to use advances in technology and organisational knowledge to optimise the system.

The main problem in responding to unknown threats (e.g. AIV in cats in Pomerania) is the grey area between non-standard risks and known threats [4, 84]. If the threat is well-defined (e.g. rabies and dirofilaria in pets of the war refugees from Ukraine or the typical HPAI in poultry), the infection control strategy can be planned in advance [2]. If rabies is suspected in a human following animal exposure, the medical doctor and the veterinarian have detailed procedures on what to do. Hazmat and CBRNE (Chemical, Biological, Radiological, Nuclear and Explosives) teams, emergency and infectious disease hospital staff and other inspectors regularly train in response (i.e. simulated outbreaks of the most likely agents) [67]. In the case of Disease X (a hypothetical case), rural doctors from the Żuławy region (Vistula agricultural zone) or epidemiologists from either one of the provincial hospitals in the Gdańsk Bay area (excluding the Tricity) may be the first to link the increase in ILI cases among their patients to the mass mortality of seagulls. Informal interdisciplinary ties between local community leaders will be crucial to defining the threat and responding smoothly [83]. Therefore, social reactions must be taken into account in mitigating epidemic threats [89].

Disease X

The current situation related to bird flu raises concerns about the possibility of another pandemic among humans, particularly in the context of the so-called Disease X. It is a term reserved for a hypothetical pathogen (most likely zoonotic virus), much more lethal than COVID-19 and capable of causing a global health crisis on an unknown scale.

Geopolitical challenges and climate change destabilize human flow systems, creating conditions for the migration of species and the development of new pathogens, pose new categories of risks to humans, animals and the environment [90]. Gdańsk (where this Journal is published) and the Tricity metropolitan area (Gdańsk, Sopot and Gdynia) in Poland, seems to be susceptible, particularly during the tourist season with an additional > 10 million visitors each summer and new problems not related to typical foodborne outbreaks [91-92]. In terms of possible spillovers and reassortments of avian influenza, the Poland's Baltic coastline (particularly the Gdańsk Bay) was identified as one of the most important hotspots in the entire Europe due to crossing of main bird migration paths [93]. Increased mobility of goods (e.g. the Gdańsk and Gdynia ports together are 4th in Europe in terms of cargo tonnage handled)

and people (planned construction of a mega airport hub in Central Poland), growing numbers of migrations (e.g. war refugees from Ukraine or flows from the Global South) and further urbanization of metropolises (increased population density) with simultaneous depopulation of the provinces create new challenges and threats. These factors have enabled the rapid spread of new diseases and may change the most likely entry point of new pathogens from Western to Eastern Europe.

The situation described above highlights the particular vulnerability of Gdańsk and the Tricity area on a micro scale (as well as the entire world on a macro scale) and aptly illustrates broader trends related to civilizational development. These trends have long been discussed in sociological literature, notably through the concept of the "risk society" detailed by the German sociologist Ulrich Beck in his 1986 book "Risk Society: Towards a New Modernity" [94]. According to Beck, a "risk society" is a modern society dominated by global threats and risks arising from technological advancement, industrial economy and modernization processes [95]. A classic example of such global risk is undoubtedly Disease X, which poses both a tangible threat and one immersed in uncertainty. It is unknown what epidemiological problem will lead to a crisis or when it will happen.

In the recently popular futurological BANI theory by Jamais Cascio, the post-pandemic world is described using four words: brittle, anxious, non-linear and incomprehensible [96]. We can view the major public health challenges through a similar lens. The COVID-19 crisis showed that the healthcare systems we considered stable and predictable, turned out to be fragile: there was a shortage of masks and disinfectants, the preventive measures failed and hospitals were closed to some extent [97]. The response to this was adaptation: the launch of telehealth services, lockdowns and restrictions. After the pandemic, there was a sense of regaining control although it is immersed in the uncertainty of anticipation of Disease X. The world of health is also non-linear. As some fields develop, others may be neglected. We are using cutting-edge science to develop gene therapies, while not conducting enough research into new groups of antibiotics. Medicine is also an increasingly complex system, susceptible to geopolitical and climate changes.

All this means that in a chaotic world, it is necessary to be as flexible as possible in taking action. Monitoring definable threats (while not closing our eyes to new ones) and preparing strategies for mitigating the risks posed by an unknown disease. This is exemplified by the case of avian influenza as the most likely agent of the upcoming crisis [98].

The potential pandemic of Disease X – there is not a question of "if" but "when" it will happen [99]. To mitigate this risk we need to enhance surveillance, strengthen biosecurity, build strong vaccination strategies and improve the communication between animal and human health agencies. Responding to new avian influenza outbreaks through a One Health approach particularly involves monitoring exposed individuals for potential infections, conducting syndromic and laboratory surveillance to identify and track cases, planning and preparing for in-depth epidemiologic investigations and evaluating the effectiveness of existing medical countermeasures (e.g. diagnostic tests: antigen, antibody and PCR), vaccines (e.g. the 100 days concept) and therapeutics (e.g. oseltamivir) all together [100].

A collaborative One Health approach is essential not only in theory. This is the lesson that we need to learn from the situation in Europe in 2023. And it has to be implemented in practice to address the complex challenges posed by avian influenza and other diseases, ensuring the protection of human health, animal welfare, and economic stability [62]. In conclusion, further discussion on the reorganization of preparedness efforts in Europe appears warranted, particularly regarding the enhancement of EWS, interdisciplinary collaboration and resource allocation for effective outbreak response.

The situation escalated in November 2024, as the H5N1 virus not only continued its spread among known mammalian hosts in the USA (including humans and companion animals) but also exhibited a concerning leap to pigs, marking the first confirmed cases within this species [101]. This development has alarmed the virology community, as recombinants of swine and avian influenza viruses pose a significant pandemic threat. The emergence of AH5N1 in pigs suggests we are edging closer to a potential pandemic scenario.

Conflict of interest

The first author was involved personally in the 2023 investigation of the epizootic outbreak among cats in the Gdańsk area, with access to internal data. However, the information provided in this article is based on publicly available sources integrated with non-classified personal communications, his own unpublished analysis and with the personal opinions of the authors.

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SHORT COMMUNICATION

Unusual acute idiopathic scrotal edema – could it be a separate disease (chronic idiopathic scrotal edema)?

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Abstract

Acute idiopathic scrotal edema (AISE) is a rare, mild and self-limiting disease. The etiology and pathogenesis of this disease remain unclear. Diagnosing AISE requires the exclusion of other scrotal disorders. We report a 48-year-old Caucasian male patient admitted to the Department of Urology with an atypical course of AISE which persisted for 12 months, despite adequate conservative treatment. Accordingly, we propose a new term, chronic idiopathic scrotal edema (CISE), to describe an extremely rare cause of bilateral scrotal edema in adults.

Keywords: scrotal edema · scrotal surgery · scrotal disorders

Citation

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Introduction

Acute idiopathic scrotal edema (AISE) is a rare, mild and self-limiting disease. Its etiology and pathogenesis are unknown. AISE is mainly found in young boys but can also occur in adult men [1-2]. Determining the diagnosis of AISE requires the exclusion of other scrotal disorders (Table 1). The onset of AISE is sudden, but the symptoms usually resolve spontaneously within 3-5 days. Unilateral enlargement of the scrotum is observed in more than half of cases [1]. Patients most often complain of pain in the scrotum and erythema of the groin [1]. Ultrasound examination reveals a swollen and thickened scrotal wall without involvement of the deeper layer structures (testis or epididymis). Hypervascularity of the scrotum (fountain sign visible in the horizontal plane) is a common symptom [2]. We present a case of an atypical course of AISE which persisted for one year, despite adequate conservative treatment. Due to the long duration the disease, we decided to treat surgically. During 5 years of follow-up, the symptoms of idiopathic scrotal edema have not recurred. Our aim was to describe an atypical course of a long-lasting idiopathic scrotal edema in an adult and to present surgery as an effective method of treatment.

Case report

A 48-year-old Caucasian male was admitted to the Department of Urology with the chief complaint of massive edema of the scrotum accompanied by pain, erythema and discomfort (Figure 1]. The symptoms began 12 months ago, resulting in loss of sexual activity due to penis buried in the edema and erectile dysfunction (15 points on the IIEF-5 (International Index of Erectile Function) questionnaire). The patient denied having allergies, previous surgeries (i.e. penile enlargement procedures) or scrotal trauma. His current medical history included hypertension, gout, obesity (BMI = 37 kg/m^2) and he was an active tobacco smoker with a 20 pack-year history). He took a variety of medications, including alpha blockers, beta blockers, calcium blockers, diuretics and sartans. The patient stated that the edema of the scrotum occurred 12 months earlier and since then has led to lower quality of life, particularly in terms of social interaction.

The patient's scrotum was significantly enlarged, with smooth, painful skin on palpation. His penis was engulfed by the swollen scrotum. The inguinal nodes were not enlarged.

Colonoscopy and computed tomography of the abdomen and pelvis were performed and did not reveal any cause of the edema was found. Ultrasonography of the scrotum revealed a positive fountain sign and scrotal wall thickness of approximately 4 cm.

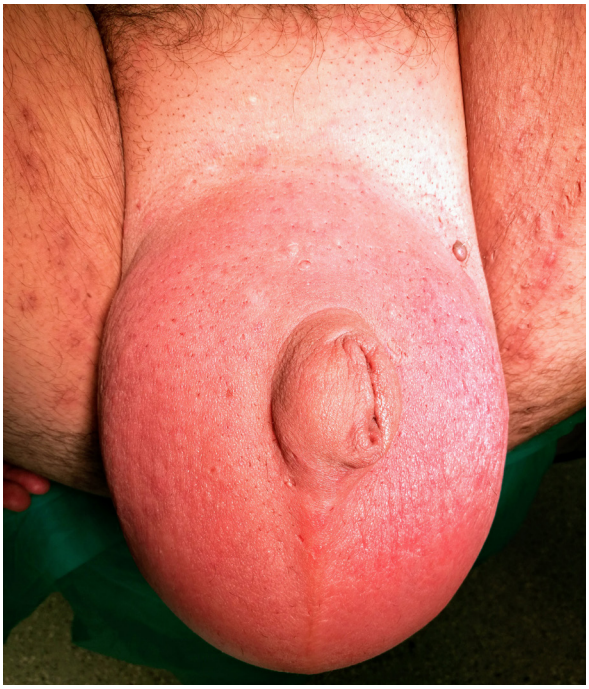

Figure 1. Massive edema of the scrotum in the course of the chronic idiopathic scrotal edema

Due to the unclear etiology of this long-lasting scrotal edema, an in-depth differential diagnosis was performed (Table 1). Microscopic examination of the incisional skin biopsy specimen taken from the scrotal wall revealed nonspecific inflammatory lesions. There was no improvement after 1 month of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihistamines and also after changing some of the medications the patient was taking in chronically. Therefore, other causes of scrotal edema were excluded.

Due to the scrotal edema and the reported discomfort, it was decided to perform scrotal surgery. The scrotum was resected and the testes were placed in the perineum. Microscopic analysis of all the collected samples revealed nonspecific inflammatory lesions in the skin and subcutaneous tissue (Figure 2). In five-years follow-up no further scrotum edema, pain or erythema was observed (Figure 3). The patient reported being sexually active with good erectile function (IIEF-5 score 23 points) and denied any problems related to testicular placement in the perineum.

Discussion

Diagnosis of AISE requires the exclusion of other scrotal disorders [1, 3-5]. As shown in Table 1, none of these tests indicated an unequivocal cause of our patient's scrotal edema. However, scrotal ultrasound examination has revealed the "fountain sign," which was first described by Geiger as highly

Table 1. The differential diagnosis for chronic idiopathic scrotal edema

Disease	Test results
Orchitis Epididymitis	Ultrasound image of the testes and the epididymis was normal.
Sexually transmitted diseases Indurated edema of scrotum	Urethral swab confirmed the presence of physiological bacterial flora and was negative for *Chlamydia* spp., *Ureaplasma* spp., *Neisseria gonorrhoeae*. VDRL test was negative.
Crohn's disease	No sign of Crohn's disease in colonoscopy
Anogenital granulomatosis	Not confirmed by histopathological examination
Erysipelas	ASO 108 IU/ml [< 250 IU/ml is normal].
Hereditary swelling associated with a quantitative deficiency (HAE type I) or functional C1 protein inhibitor (HAE type II)	Concentrations of C4 protein and C1 protein inhibitor were normal (the test was performed twice).
Filariasis	No eosinophilia in laboratory tests. The histopathological examination was negative for *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*.
AISE	The symptoms remained for > 7 days despite adequate treatment

AISE – acute idiopathic scrotal edema, ASO – anti-streptolysin O, HAE – hereditary angioedema, VDRL – Venereal Disease Research Laboratory test

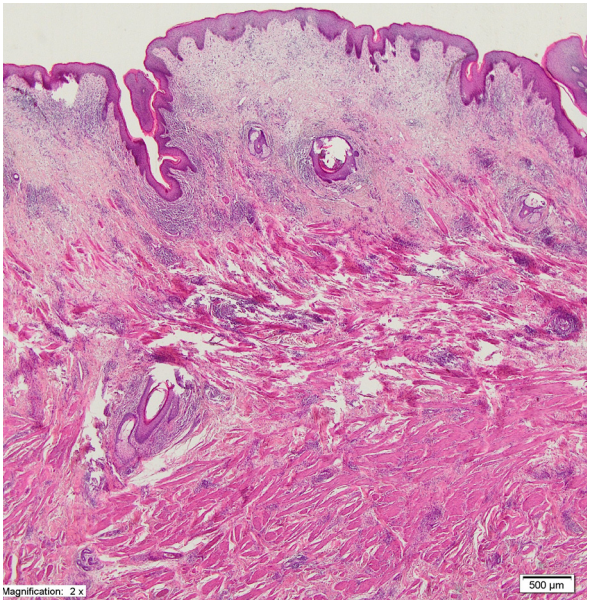

Figure 2. The histopathological examination revealed numerous, dilated lymphatic vessels, fibrosis within the dermis and foci of chronic inflammatory infiltration

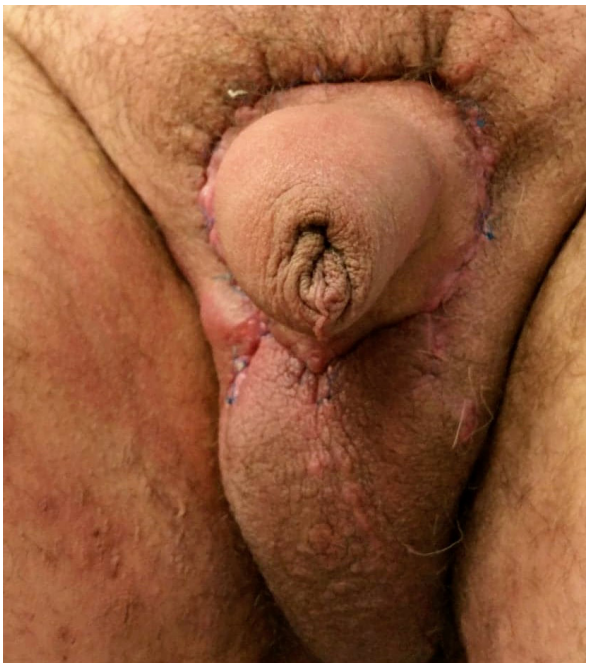

Figure 3. Outpatient follow-up

suggestive of the diagnosis of AISE [2-3]. Other possible ultrasound findings in AISE include reactive hydrocele and enlargement of inguinal nodes [3].

Sudden onset and spontaneous regression of scrotal edema within 3-5 days is typical for AISE. Conservative treatment including bed rest and activity restriction, NSAIDs, antibiotics and antihistamines have been established as the treatment of choice [1, 3-5]. As stated by Santi et al., there are no cases of AISE with duration of more than 7 days [1]. In all cases of AISE reported to date, surgical treatment was described as the wrong choice [1, 3-5]. However, we would like to ask the question: what should be the next step when the scrotal edema persists despite adequate conservative treatment?

Conclusions

Based on the case described above, we suggest a new term, Chronic Idiopathic Scrotal Edema (CISE), to describe an extremely rare cause of bilateral scrotal edema in adults. The main differences between acute and chronic scrotal edema (AISE vs. CISE) are the duration of the disease (< 7 days vs. ≥ 7 days) and the method of treatment (conservative vs. surgery). Further studies are needed to confirm our findings.

Statement of ethics

The patient provided written informed consent to publish this case report.

Conflict of interest

The authors declare that they have no conflicts of interest.

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RESEARCH ARTICLE

Safety and efficacy of the Oxford--AstraZeneca vaccine against SARS-CoV-2 after 2nd and 3rd dose in adults: a cross-sectional study

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Abstract

Background: The rapid global spread of the coronavirus SARS-CoV-2 and the lack of established therapeutic choices led to development of several vaccines. Our aim was to investigate the safety and effectiveness of the Oxford--AstraZeneca adenovirus vectored vaccine against SARS-CoV-2 breakthrough infections in people who were vaccinated with 2 or 3 doses of it. **Methods:** This cross-sectional study was conducted from February 2021 to September 2021 on 997 people, who had received at least 2 doses of the Oxford-AstraZeneca vaccine. Demographic and clinical data were recorded using a questionnaire. The effectiveness of the vaccine was calculated based on the percentage of vaccinated people with confirmed and probable cases of SARS-CoV-2 infection. SPSS software was used for data analysis, and a significance level of $p < 0.05$ was chosen. **Results:** After vaccination with the 2nd and 3rd doses, 355 (35.6%) and 26 (8.3%) participants contracted the SARS-CoV-2 infection, respectively. Breakthrough infection after the 2nd dose was significantly higher in females ($p < 0.001$), those with older age ($p = 0.021$), diabetes ($p = 0.003$) and hypertension ($p < 0.001$). Additionally, a significant correlation was found between SARS-CoV-2 infection after the 3rd dose and chronic kidney disease ($p = 0.022$) and a history of infection after the second dose ($p < 0.001$). The prevalence of vaccine side effects after the 2nd and 3rd doses was 51.7% and 13.4%, respectively. **Conclusions:** The effectiveness of the Oxford-AstraZeneca vaccine in preventing SARS-CoV-2 increased from 64.4% after 2 doses to 91.7% after the 3rd dose, therefore it is recommended to administer a 3rd dose to ensure strong immunity against SARS-CoV-2. Based on our data the safety of this vaccine is acceptable.

Keywords: SARS-CoV-2 · Oxford-AstraZeneca · efficacy · safety · adverse effects

Citation

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Introduction

As of November 3rd 2024 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 776.63 million people and caused 7.071 million deaths globally [1]. Effective long-term control of SARS-CoV-2 relies on achieving herd immunity within the population and vaccination is recommended as a safe and effective method to attain such immunity [2-5]. Both the US Food and Drug Administration (FDA) and the World Health Organization (WHO) guidelines state that they will approve a new vaccine for a pandemic virus if it demonstrates at least 50% efficacy [6-7]. In response, several anti-SARS-CoV-2 vaccines were developed in a shorter time [8]. Several studies have demonstrated that SARS-CoV-2 vaccines provide significant short-term protection, thus reducing the severity of the disease and lowering mortality rates [9-11].

As suggested by its name, the Oxford-AstraZeneca vaccine ChAdOx1 nCoV-19 (AZD1222) was developed by AstraZeneca and Oxford University. It is a chimpanzee adenoviral vector vaccine primarily distributed in India, Brazil and the United Kingdom [12-13]. This vaccine has demonstrated acceptable efficacy and safety in adults [14]. Due to its lower cost and simpler logistical requirements compared to mRNA vaccines, the Oxford-AstraZeneca (OAZ) vaccine has seen wider use particularly in the low- and middle-income countries of South America, Africa and Asia [9, 15]. Some studies have shown that 1 and 2 doses of the OAZ vaccine are moderately effective against mild coronavirus disease 2019 (COVID-19) and highly effective against severe cases [13, 16-17]. The OAZ vaccine's effectiveness against symptomatic disease peaks at ~ 50%, while its effectiveness against hospitalization reaches 85-90% [16]. However, randomized controlled trials have shown that the vaccine effectiveness waning over time, as shown by decreased levels of neutralizing antibodies [18-19]. Breakthrough infections have also been reported in people who received 2 doses of vaccine [18-19]. Another study indicated that antibody levels following thePfizer–BioNTech (mRNA), Moderna (mRNA) and OAZ vaccines can persist for at least 6 months but tend to diminish over time [3]. Thus, an urgent 3rd dose of the SARS-CoV-2 vaccine is necessary to control the increasing number of infections [20]. For instance, some studies have demonstrated that a 3rd dose of the Pfizer-BioNTech vaccine offers enhanced protection against infection and reinforces the immunity achieved after the initial 2 doses [18, 21-22]. In the case of OAZ vaccine, most studies on its efficacy and safety focus on the 1st and 2nd doses, with limited research on the booster dose's effectiveness [15, 20]. Therefore, the aim of our study was to investigate in a sample of Iranian people the efficacy of the OAZ vaccine in preventing probable and confirmed COVID-19 breakthrough infections within 6 months after the 2nd and 3rd doses, to evaluate this vaccine's adverse effects and to explore the association between demographic and clinical variables to identify potential risk factors for COVID-19 breakthrough infections among those vaccinated with that vaccine.

Material and methods

This cross-sectional study was conducted in collaboration with Birjand University of Medical Sciences and healthcare facilities in the South Khorasan province (Iran). We enrolled 997 participants who were > 18 years of age and received at least 2 doses of the OAZ vaccine from February 2021 to September 2021. Exclusion criteria were: < 18 years of age, vaccination with a different vaccine type, dementia, pregnancy and lacking of cooperation with the research staff. We performed random cluster sampling. Then, the effectiveness of the OAZ vaccine in preventing COVID-19 was evaluated in people who received 2 doses of it.

Based on clinical manifestations, the 2020 interim WHO guideline described patients with COVID-19 were classified into 3 main groups: suspected case, probable case and confirmed case [23]. The guideline also allowed countries to adapt these definitions based on their specific health and epidemiological conditions [23-24]. Based on this WHO guideline, the Ministry of Health, Treatment and Medical Education of the Islamic Republic of Iran issued its recommendations for the treatment and control of SARS-CoV-2 infections and in our study, patients were classified accordingly [25] (Table 1).

Table 1. Classification of SARS-CoV-2 infections used in this study and based on [25]

Suspected case	A person with a history of dry cough, chills, sore throat, shortness of breath, fever or severe respiratory symptoms that cannot be accounted for by another etiological component.
Probable case	– Person with COVID-19 symptoms and radiological signs of pneumonia and ground-glass opacities. – Patient with pneumonia whose condition worsens despite treatment. – Patient who had symptoms similar to COVID-19 and died without any SARS-CoV-2 PCR test resultson record.
Confirmed case	SARS-CoV-2 infection confirmed with laboratory testing

Outcomes

The main outcome we assessed in this study was the rate of SARS-CoV-2 breakthrough infection (defined as the percentage of vaccinated people who had confirmed or probable SARS-CoV-2 infection) after vaccination with the 3rd dose of the OAZ vaccine and we compared it with the results after the 2nd dose of the vaccine. In addition, the severity of infection and the rate of hospital admissions were studied after each vaccine dose. The safety outcome were the local and systemic reactions that occurred within 14 days after each dose (reported by participants using a questionnaire).

Data sources

Demographic details, contact numbers, addresses, the type of COVID-19 vaccine administered, the total number of doses received by each person and the intervals between vaccine doses were extracted from the Integrated Health System (Samaneh Yekparche-ye Behdashti) in collaboration with the Health and Treatment Deputy of Birjand University of Medical Sciences. In the next stage, 997 people who met the inclusion criteria were randomly selected. Next, we contacted them via phone call and explained the purpose of the study and how to participate. Those who gave their consent to participate in this study were given a questionnaire containing 3 parts: demographic and clinical information (e.g. age, sex, level of education, occupation, weight, height, blood type), risk factors and habits (e.g. comorbidities, smoking, drug use) and vaccination-related information (e.g. the number of vaccine doses, symptoms after vaccination). Additional questions were asked about history of SARS-CoV-2 infection before and after vaccination, method of diagnosing SARS-CoV-2 infection before and after vaccination.

Ethics and oversight

The study protocols and questionnaire were approved by the Local Ethics Committee at each center. Informed consent was obtained from all subjects involved in the study. This study was carried out in accordance with the Helsinki Declaration principles and approved by the University of Sistan and Baluchestan ethics committee (approval ID: IR.USB.REC.1400.105).

Statistical Analysis

After collecting and recording the raw data, we used the IBM SPSS software version 26.0 (Armonk, NY, United States) to calculate the Pearson's chi-square test. The normality of the data was checked using the Kolmogorov-Smirnov test. Statistical differences between groups were determined using non-parametric tests (Mann-Whitney U test and Kruskal-Wallis H test) due to its non-normal distribution. A significance level of $p < 0.05$ was considered statistically significant. The results were presented as mean ± standard deviation (SD) and frequency (percentage).

Results

The demographic and clinical characteristics of the participants are described in Table 2. Among the 997 participants who were vaccinated with 2 doses of the OAZ vaccine, 536 (53.8%) were men, and 461 (46.2%) were women. The median age of the participants was 50.96 ± 15.03 years and the age range of subjects was between 20 and 96 years old. Among the participants who had received 2 doses of the OAZ vaccine, 380 (38.1%) had comorbidities, most frequently hypertension (20.8%) and diabetes mellitus (18.4%).

SARS-CoV-2 infection before and after vaccination with the 2nd and 3rd doses

Among the people who received the 2nd doses of the vaccine, 29.6% had a history of SARS-CoV-2 infection before vaccination. After the 2nd dose, 355 (35.6%) participants were infected within an average duration of 110.2 ± 39.0 days. Only 3 (0.85%) participants needed hospitalization, whereas the rest of them (n = 352, 99.15%) were treated at home. Additionally, 313 (31.4%) participants were vaccinated with 3 doses of the OAZ vaccine. Among them, 26 people (8.3%) contracted the SARS-CoV-2 infection after an average of 41.7 ± 16.9 days following the 3rd dose of the vaccine and none required hospitalisation (Table 3).

Effectiveness of the OAZ vaccine in preventing SARS-CoV-2 infection

The effectiveness of the OAZ vaccine was calculated based on the percentage of vaccinated people who were infected with confirmed and probable cases of SARS-CoV-2 infection after vaccination. Among the 355 participants who were diagnosed with SARS-CoV-2 after receiving the 2nd vaccine dose, 96 (9.6%) were diagnosed with confirmed SARS-CoV-2 infection and 259 (26.0%) were diagnosed with probable SARS-CoV-2 infection. Likewise, out of the 26 participants who were infected with SARS-CoV-2 after receiving the 3rd vaccine dose, 7 (2.2%) had confirmed SARS-CoV-2 infection, while 19 (6.1%) participants had probable SARS-CoV-2 infection. These results indicate that the OAZ vaccine efficacy in preventing COVID-19 has increased from 64.4% after the 2nd dose to 91.7% after the 3rd dose (Table 3).

Table 2. Demographic and clinical characteristics of the participants

Characteristics	People vaccinated with 2 doses of the OAZ vaccine	People vaccinated with 3 doses of the OAZ vaccine
Number (n,%)	997	313
Sex (n, %)		
Females	461 (46.2%)	145 (46.3%)
Males	536 (53.8%)	167 (53.4%)
Missing data	-	1 (0.3%)
Mean age (years)	50.96 ± 15.03	53.41 ± 16.64
Age range (years)	20-96	20-86
Mean height (cm)	166.43 ± 8.93	166.37 ± 9.32
Height range (cm)	145-195	145-190
Mean weight (kg)	70.33 ± 14.65	70.20 ± 14.53
Weight range (kg)	30-163	30-120
Education* (n, %)		
Illiterate	128 (12.8%)	53 (16.9%)
primary to secondary school	506 (50.8%)	151 (48.2%)
university graduates	361 (36.2%)	108 (34.6%)
Missing data	2 (0.2%)	1 (0.3%)
Job* (n, %)		
Unemployed	8 (0.8%)	1 (0.3%)
Manual laborer	52 (5.2%)	21 (6.7%)
Office worker	302 (30.3%)	84 (26.8%)
Housewife	310 (31.1%)	104 (33.2%)
Self-employed	176 (17.7%)	41 (13.1%)
Retired	131 (13.1%)	58 (18.6%)
Student	16 (1.6%)	4 (1.3%)
Missing data	2 (0.2%)	0 (0%)
Blood group* (n, %)		
A+	383 (38.4%)	120 (38.3%)
A-	23 (2.3%)	7 (2.2%)
B+	231 (23.2%)	65 (20.8%)
B-	23 (2.3%)	11 (3.6%)

* Some of this data is missing.
† Other underlying diseases included cancer, arthritis, liver diseases, autoimmune diseases, hyperthyroidism, hepatitis B and allergies.
CKD – chronic kidney disease

Table 2. Demographic and clinical characteristics of the participants (continued)

Characteristics	People vaccinated with 2 doses of the OAZ vaccine	People vaccinated with 3 doses of the OAZ vaccine
AB+	89 (8.9%)	28 (8.9%)
AB-	3 (0.3%)	1 (0.3%)
O+	177 (17.8%)	61 (19.5%)
O-	30 (3%)	12 (3.8%)
Missing data	38 (3.8%)	8 (2.6%)
Comorbidities (n, %)		
None	617 (61.9%)	183 (58.5%)
Hypertension	207 (20.8%)	81 (25.9%)
Diabetes mellitus	183 (18.4%)	63 (20.1%)
Cardiovascular diseases	101 (10.1%)	32 (10.2)
Hyperlipidemia	32 (3.2%)	9 (2.9%)
CKD	25 (2.6%)	8 (2.6)
Cardiopulmonary disease	21 (2.1%)	5 (1.6)
Hypothyroidism	11 (1.1%)	3 (1%)
Other†	38 (3.8%)	12 (3.8%)

* Some of this data is missing.
† Other underlying diseases included cancer, arthritis, liver diseases, autoimmune diseases, hyperthyroidism, hepatitis B and allergies.
CKD – chronic kidney disease

Table 3. Demographic and clinical characteristics of the participants

		2 doses	3 doses
	Number of participants	997	313
	History of SARS-CoV-2 infection before the vaccination (%)	295 (29.6)	229 (73.16)
SARS-CoV-2 infection after vaccination with OAZ	Non-infectious cases (%)	642 (64.4)	287 (91.7)**
	Confirmed infection (%)	96 (9.6)	7 (2.2)
	Probable infection (%)	259 (26.0)	19 (6.1)
	Total number of infections (%)	355 (35.6)*	26 (8.3)**
	Average time to infection (days)	110.2 ± 39.0	41.7 ± 16.9
	Hospitalisation (%)	3 (0.85)	0
	Outpatient treatment (%)	352 (99.15)	26 (100)

*Percentage of the total number (997 people)
**Percentage of the total number (313 people)

Adverse effects

515 (51.7%) participants had ≥ 1 adverse effect after the 2nd dose of the OAZ vaccine, the most common of which included injection site pain (32.5%), fatigue (30.1%), cough (28.7%) and fever (28.1%). Whereas 42 (13.4%) participants had adverse effects after the 3rd dose of the vaccine, most commonly injection site pain (10.2%), swelling at the injection site (6.4%), local redness (4.2%) and cough (3.5%) (Table 4).

Analytical results

In our study we found that SARS-CoV-2 infection rates after 2 doses of the OAZ vaccine were significantly higher in females ($p < 0.001$), participants with comorbidities ($p = 0.012$), particularly diabetes ($p = 0.003$) and hypertension ($p < 0.001$), as well as among those working outside the home ($p = 0.021$). Additionally, the average age of the infected participants was significantly higher than that of non-infected individuals ($p = 0.021$). After vaccination with the 3rd dose, the rate of COVID-19 infection was significantly higher in participants with chronic kidney disease (CKD) ($p = 0.022$) and those who had a history of COVID-19 infection after the second dose of the vaccine ($p < 0.001$) (Table 5).

Our analysis revealed a significant correlation between confirmed and probable SARS-CoV-2 infection after 2 vaccinations with the age group ($p = 0.008$), occupation ($p < 0.001$) and comorbidities ($p < 0.001$). However, no significant correlation was observed among males and females ($p = 0.106$). The highest number of confirmed and probable SARS-CoV-2 cases was reported in the group < 40 years and > 60 years of age, respectively. Conversely, no significant difference was observed in the subgroups (sex, age, employment, underlying diseases) in terms of confirmed and probable infection after the 3rd dose (Table 6).

Table 4. OAZ vaccine adverse effects by dose

	After 2nd dose	After 3rd dose
Number of participants with adverse effects (n, %)	515 (51.7%)	42 (13.4%)
Total number of adverse effects	Range (1-4)	Range (1-2)
Injection site pain	324 (32.5%)	32 (10.2%)
fatigue	280 (28.1%)	6 (1.9%)
cough	286 (28.7%)	11 (3.5%)
fever	280 (28.1%)	6 (1.9%)
anxiety and poor sleep quality	162 (16.2%)	-
swelling	102 (10.2%)	20 (6.4%)
local redness	95 (9.5%)	13 (4.2%)
nausea	86 (8.6%)	3 (1%)
vomiting	27 (2.7%)	2 (0.6%)
diarrhea	36 (3.6%)	-
smell and hearing disorders	22 (2.2%)	-
loss of smell	15 (1.5%)	-
lymphocytopenia	3 (0.3%)	-
conjunctivitis	1 (0.1%)	-
pulmonary involvement in CT scan images	10 (1%)	-

CT – computer tomography

Table 5. Comparison of independent variables in the case of contracting and not contracting SARS-CoV-2 after the 2nd and 3rd doses of the OAZ vaccine

Variable	After the 2nd dose			After the 3rd dose		
	infection	No infection	p-value	infection	No infection	p-value
Age, (Mean ± SD)	51.17 ±14.33	50.59 ± 16.25	**0.021**	54.81 ± 17.07	53.28 ± 16.62	0.732
BMI, (Mean ± SD)	25.45 ± 4.66	25.14 ± 4.36	0.495	25.77 ± 3.70	25.30 ± 4.89	0.441
Days between the 1st and 2nd doses, (Mean ± SD)	82.44 ± 14.89	82.66 ± 8.90	0.113			
Days between the 2nd and 3rd doses, (Mean ± SD)				131.63 ± 16.33	140.52 ± 22.58	0.393
Sex						
Male (%)	160 (45.1)	375 (58.6)	**< 0.001**	17 (65.4)	150 (52.4)	0.225
Female (%)	195 (54.9)	265 (41.4)		9 (34.6)	136 (47.6)	
Education						
Less than university education (%)	226 (63.7)	408 (63.7)	0.978	18 (69.2)	186 (65.0)	0.830
University degree (%)	129 (36.3)	232 (36.3)		8 (30.8)	100 (35)	
Blood group						
A (%)	131 (38.9)	276 (44.2)	0.169	13 (52.0)	114 (40.7)	0.285
B (%)	103 (30.6)	151 (24.2)		5 (20)	71 (25.4)	
AB (%)	33 (9.8)	59 (9.5)		0 (0.0)	29 (10.4)	
O (%)	70 (20.8)	138 (22.1)		7 (28.0)	66 (23.6)	
Rh						
Positive (%)	303 (89.9)	578 (92.5)	0.182	22 (88.0)	252 (90.0)	0.729
Negative (%)	34 (10.1)	47 (7.5)		28 (12.0)	3 (12.0)	
Comorbidities (%)	154 (43.4)	226 (35.2)	**0.012**	13 (50.0)	117 (40.8)	0.409
Diabetes Mellitus (%)	83 (23.4)	100 (15.6)	**0.003**	9 (34.6)	54 (18.8)	0.071
Cardiovascular disease (%)	43 (12.1)	58 (9.0)	0.126	5 (19.2)	21 (80.8)	0.164
Hypertension (%)	97 (27.3)	(17.2)	**< 0.001**	8 (30.8)	73 (25.4)	0.640
Cancer (%)	4 (1.1)	3 (0.5)	0.255	1 (3.8)	3 (1.0)	0.294
Cardiopulmonary disease (%)	6 (1.7)	15 (2.3)	0.647	0 (0.0)	5 (1.7)	1.000

BMI – body mass index; CKD – chronic kidney disease; Rh – Rhesus (Rh) factor
Statistically significant results are printed in **bold**.

Table 5. Comparison of independent variables in the case of contracting and not contracting SARS-CoV-2 after the 2nd and 3rd doses of the OAZ vaccine (continued)

Variable	After the 2nd dose			After the 3rd dose		
	infection	No infection	p-value	infection	No infection	p-value
Arthritis (%)	1 (0.3)	2 (0.3)	1.000	0 (0.00)	1 (0.3)	1.000
CKD (%)	10 (2.8)	15 (2.3)	0.675	3 (11.5)	5 (1.7)	**0.022**
Hepatic (%)	4 (1.1)	4 (0.6)	0.465	0 (0.00)	1 (0.3)	1.000
Autoimmune (%)	3 (0.8)	4 (0.6)	0.704	1 (3.8)	2 (0.7)	0.230
Hyperlipidemia (%)	14 (3.9)	18 (2.8)	0.351	2 (7.7)	7 (2.4)	0.166
Hypothyroidism (%)	2 (0.6)	9 (1.4)	0.345	0 (0.00)	3 (1.0)	1.000
Hyperthyroidism (%)	1 (0.3)	2 (0.3)	1.000	0 (0.00)	0 (0.00)	-
Hepatitis B (%)	2 (0.6)	2 (0.3)	0.619	0 (0.00)	0 (0.00)	-
Allergy (%)	2 (0.6)	2 (0.3)	0.619	0 (0.00)	3 (1.0)	1.000
History of COVID-19 before vaccination						
Yes (%)	112 (31.5)	183 (28.5)	0.346	15 (57.7)	214 (74.6)	0.069
No (%)	243 (68.5)	459 (71.5)		11 (42.3)	73 (25.4)	
History of COVID-19 after 2 doses of vaccine						
Yes (%)				25 (96.2)	99 (34.5)	**< 0.001**
No (%)				1 (3.8)	188 (65.5)	
Job						
Working outside the home (%)	168 (47.4)	281 (43.8)	0.285	12 (46.2)	151 (52.6)	0.335
Working at home (%)	185 (52.4)	361 (56.2)		14 (53.8)	136 (47.4)	
Unemployed (%)	0 (0.0)	8 (1.2)	**0.021**	0 (0.00)	1 (0.3)	0.733
Manual laborer (%)	137 (38.8)	173 (26.9)		3 (11.5)	18 (6.3)	
Office worker (%)	112 (31.7)	190 (29.6)		8 (30.8)	76 (26.5)	
Housewife (%)	19 (5.4)	33 (5.1)		6 (23.1)	98 (34.1)	
Self-employed (%)	48 (13.6)	128 (19.9)		3 (11.5)	38 (13.2)	
Retired (%)	31 (8.8)	100 (15.6)		6 (23.1)	52 (18.1)	
Student (%)	6 (1.7)	10 (1.6)		0 (0.00)	4 (1.4)	

BMI – body mass index; CKD – chronic kidney disease; Rh – Rhesus (Rh) factor
Statistically significant results are printed in **bold**.

Table 6. Comparison of confirmed and probable coronavirus infection rates with various parameters after the 2nd and 3rd doses of the OAZ vaccine

		After the 2nd dose				After the 3rd dose			
Variable	**Condition**	Total Number	Confirmed infection (%)	Probable infection (%)	**p-value**	Total Number	Confirmed infection (%)	Probable infection (%)	**p-value**
Sex	Male	535	50 (9.3)	110 (20.6)	0.106	167	4 (2.4)	13 (7.8)	0.592
	Female	460	46 (10.0)	149 (32.4)		145	3 (2.1)	6 (4.1)	
Age	20-39	189	29 (15.3)	60 (31.7)	**0.008**	69	3 (4.3)	2 (2.9)	0.178
	40-59	549	50 (9.1)	109 (19.9)		127	2 (1.6)	9 (7.1)	
	≥60	259	17 (6.6)	90 (34.7)		117	2 (1.7)	8 (6.8)	
Job type	Working outside the home	546	65 (11.9)	120 (22.0)	**< 0.001**	150	5 (3.3)	9 (6.0)	0.275
	At home	449	30 (6.7)	138 (30.7)		163	2 (1.2)	10 (6.1)	
Comorbidities	Yes	380	25 (6.6)	129 (33.9)	**< 0.001**	130	2 (1.5)	11 (8.5)	0.185
	No	617	130 (11.5)	130 (21.1)		183	5 (2.7)	8 (4.4)	

Discussion

Public trust and confidence in SARS-CoV-2 vaccines based on assessments of their effectiveness are crucial for the long-term success of vaccination. Due the emergency use authorization, the clinical trials and adverse effect investigations for SARS-CoV-2 vaccines were significantly shorter than for other vaccines. Therefore, it is vital to conduct large-scale studies across populations of various countries to gain a better understanding of the SARS-CoV-2 vaccines' effectiveness [17]. Vaccine effectiveness is a measurement of disease incidence reduction in vaccinated individuals compared to those who are not vaccinated. This evaluation is typically performed under optimal conditions (e.g. in clinical trials) and the results can vary across populations [26]. Our results showed that the OAZ vaccine's effectiveness against breakthrough infections and hospitalisation after the 2nd dose was 64.4% and 99.15%, respectively. In line with our results, in a study conducted in Brazil, South Africa and the UK it was found that the effectiveness of the OAZ vaccine against COVID-19 was 70.4% after 2 doses [16]. When a low dose was followed by a standard dose, the efficacy increased to 90.0% [16]. In an Iraqi study, 6.71% of participants contracted the SARS-CoV-2 infection, as determined by a positive PCR test, 14 days after vaccination with the 2nd dose of the OAZ vaccine, which is consistent with the 9.6% confirmed cases in our study. Mirroring our findings, none of the infected participants required hospitalisation and no deaths were reported [27]. In contrast to our results, in other studies, the overall efficacy against SARS-CoV-2 variants after the 2nd dose was higher: 73.73%, 74.0% in the United States, Chile, and Peru and 84.4% in Iran, whereas the overall efficacy against hospitalisation and death were lower than in our study [10, 17, 28]. Another study from Iran indicates that after vaccination with 2 doses of the OAZ vaccine, its maximum effectiveness in preventing regular hospitalisations and deaths is around 98% and 92%, respectively. These findings are consistent with ours [11]. Overall, the efficacy of the OAZ vaccine after the 2nd dose in our study was somewhat lower compared to most previous studies. However, its estimated efficacy in preventing hospitalisations was higher than in other studies. Factors such as study design, methodology, age distribution, demographic characteristics and the increasing prevalence of different SARS-CoV-2 variants all can influence the results regarding the effectiveness of vaccines in different studies [19].

In our study, the effectiveness of the OAZ booster dose against symptomatic disease and hospitalisation was 91.7% and 100%, respectively. It was demonstrated in a group of 177 participants from Bangkok, Thailand that administering either the OAZ or the Pfizer–BioNTech vaccine after 2 doses of the inactivated vaccine (Sinovac) can induce an immune response, including both IgA anti-spike and IFN-γ stimulation [20]. In the British population, the absolute effectiveness of the Pfizer-BioNTech or Moderna booster against symptomatic disease ranged from 94% to 97%, consistently across all age groups. For preventing hospitalisation or death, the absolute effectiveness of the Pfizer-BioNTech booster was approximately 97% to 99% across all age groups [21]. A study from England reported that the OAZ booster enhanced protection against symptomatic disease in both younger and older adults, counteracting the decline in immunity observed 25 weeks after the 2nd dose. Also, the booster doses of the OAZ and Pfizer-BioNTech vaccines significantly increased protection against symptomatic disease following infection with the Omicron variant of SARS-CoV-2, with effectiveness rates of 66.1% and 68.5% in older adults, respectively [15]. Additionally, the protection against hospitalisation peaked at 82.3% for OAZ and 90.9% for Pfizer-BioNTech [15]. Overall, previous studies indicate that a 3rd dose of an approved COVID-19 vaccine is effective in preventing COVID-19, including severe cases [15, 20-21, 29]. This finding is supported by data from the current study. However, there is limited information on the actual effectiveness of 3rd doses across different vaccines. The effectiveness of the third dose can vary depending on factors such as the specific vaccine used, the interval between the second and third doses, population characteristics, study design and the methods used to measure vaccine effectiveness. Additionally, adjustments for vaccine effectiveness may also influence the results [29].

Overall, participants in our study reported mild to moderate adverse reactions that did not require hospitalisation nor caused death. These findings align with those of other studies [13, 28, 30]. In a study from Iraq the adverse effects after the 2nd dose of the OAZ vaccine were reported in 12.45% of participants, which was lower than in our study [27]. Additionally, in the aforementioned study, the most common adverse effects after the 2nd dose were fever, pain at the injection site and myalgia, which is different than in our study [27]. In contrast to other authors, we did not report any uncommon symptoms e.g. excessive sweating, enlarged lymph nodes, loss of appetite, confusion thrombosis and thrombocytopenia [4, 9, 15]. On the other hand, we reported less frequent adverse effects e.g. conjunctivitis, lymphocytopenia, pulmonary involvement (diagnosed in CT scan images), loss of smell and hearing disorders, which have not been reported in other studies. In a study from Iran, the most common adverse effects after the 2nd dose of the OAZ vaccine were injection site pain (69.2%), headache (46.2%), fever (38.5%) and local stiffness at the injection site (23.1%). Additionally, 54.2% of the participants reported ≥ 1 adverse effect from the OAZ vaccine after the 2nd dose, which is consistent with the results of the present study [30]. In a prospective cohort study Zare et al. showed that after the second dose of the OAZ vaccine the local symptoms included pain (48.5%), tenderness (31.5%), firmness (6.3%) and swelling (4.4%), whereas the systemic symptoms were not life-threatening and included fever (43.3%), muscle pain (45.9%), joint pain (34.4%), chills (37.0%) and malaise (36.7%) [31]. The prevalence of fever in their study was higher than in ours (43.3% vs. 28.1%), but swelling was reported less than in our study (4.4% vs. 10.2% respectively). In another study, Sinaei et al. reported that the most common side effects after the 2nd dose of OAZ vaccine were injection site reaction (22.2%), fever and chills (21.5%), neurological symptoms (11.5%) and gastrointestinal symptoms (5%) [32]. Overall, adverse events reported after the second dose in the current study were relatively similar to those in most studies. Injection site pain and fever were the most commonly reported adverse events after the 2nd dose of OAZ vaccine in all reports.

Studies on adverse effects after the 3rd dose of vaccines are limited. Amer et al. reported that the prevalence of the adverse effects after 1st, 2nd and booster dose of the OAZ vaccine was respectively 23%, 22% and 3%, which was significantly different from our study [33]. Also, in contrast with our study, Yadegarynia et al. reported the prevalence of vaccine side effects increased after the 3rd dose compared to the second dose of the OAZ vaccine (57.8% vs. 48.2% respectively) and the most common side effect after the 3rd dose of the vaccine was myalgia (45.6%), followed by fever (39.9%), chills (37.3%) and headache (29.1%) [34]. The differences in the reported adverse effects can be attributed to the demographic and genetic characteristics of the studied population, the sample size and the study design [27].

According to our results, SARS-CoV-2 infection after vaccination with 2 doses of the OAZ vaccine was significantly associated with female sex, older age, and having diabetes and hypertension. Regarding the link between female sex and long COVID syndrome, Bai et al. reported that over half of COVID-19 patients experienced ongoing symptoms, with female sex being a significant factor [35]. In contrast to our findings, some studies have reported that the prevalence and severity of COVID-19 are higher in men [36-38]. On the other hand, Hossein et al. did not find significant relationship between sex and the rate of SARS-CoV-2 infection after the 2nd dose of OAZ vaccine [27]. However, the effects of COVID-19 can vary depending on factors such as socioeconomic status, ethnicity and geographic location [5]. Numerous studies have demonstrated a link between advanced age and comorbidities such as diabetes, hypertension, and CKD with the incidence and severity of COVID-19 [36-37, 39]. It is well-established that pa-

tients with diabetes have a heightened risk of infections, partly due to hyperglycemia-induced immune dysfunction [39]. Researchers in Wuhan (China) identified hypertension as the most prevalent comorbidity among COVID-19 patients, followed by diabetes and coronary artery disease. Additionally, older age was correlated with increased COVID-19 severity and mortality [36]. In another study, it was found that age ≥ 65, hypertension and diabetes were statistically more common in critical patients compared to non-critical ones [38]. However, Hussein et al. did not observe any significant correlation between age and post-vaccination infection rates [27]. Additionally, our results indicated that the incidence of contracting SARS-CoV-2 after the 2nd vaccine dose was higher among individuals working outside the home compared to those working at home. This is likely because they had a greater risk of exposure to viral particles due to their interactions with other people, however more studies are needed to confirm this conclusion.

In our sample, the rate of SARS-CoV-2 infection after vaccination with the OAZ booster dose was higher in individuals who had a history of infection following the 2nd dose, as well as in those with chronic kidney disease (CKD). In a study by Hall et al., 7.6% of participants experienced a primary infection and 0.6% experienced a secondary infection after vaccination with the Pfizer BioNTech and OAZ vaccines [40]. Research from Belgium indicated that vaccinated individuals with a history of SARS-CoV-2 infection had a significantly lower risk of new infections and symptoms, similarly to those who received an mRNA booster dose [41]. These findings contrast with our results and a possible explanation for this could be that individuals with a history of SARS-CoV-2 infection before receiving a booster vaccination were not very diligent in following health protocols (e.g. social distancing and wearing masks). Further studies are needed to confirm this hypothesis.

Previous studies have demonstrated that patients with CKD might experience elevated levels of pro-inflammatory cytokines, resulting in increased oxidative stress during a SARS-CoV-2 infection which can ultimately lead to pneumonia. Those studies have identified kidney diseases as a risk factor for the severe course of COVID-19 [37-39]. In our study, a significant relationship was observed between confirmed and probable cases of COVID-19 infection after the 2nd dose of the vaccine and factors such as age, type of work and comorbidities. The majority of confirmed cases were reported among individuals aged 20 to 39 years, those working outside the home, and those without comorbidities. This could be because people in the above-mentioned group are among the most active in the community and are more exposed to SARS-CoV-2. They are also more likely than older people with comorbidities to follow health protocols less carefully. However, more studies are needed to confirm this theory.

Limitations

Our study has some limitations. First, there is a lack of a control group or comparisons with other vaccines. Second, the weaknesses of the cross-sectional design of this study did not allow us to assess incidence, to make a causal inference, to follow up participants over time. In addition, our study is susceptible to sampling bias (e.g. non-response bias and recall bias). Third, we study included only participants > 18 years old and excluded children, adolescents and pregnant women, therefore our results may not be generalized to these populations. We did not investigate cellular and humoral immunity, which is another limitation in accurately assessing the effectiveness of the OAZ vaccine against SARS-CoV-2. Furthermore, we did not evaluate the actual effectiveness of vaccines against different strains of SARS-CoV-2. Self-reported data about adverse effects may also be prone to error, particularly because they were reported over a relatively short follow-up period.

Conclusions

In our study sample the OAZ vaccine was effective in preventing severe SARS-CoV-2 infection and hospitalisation after 2 doses. However, its effectiveness appears to decrease about 3-4 months after the 2nd dose, highlighting the need for a booster dose. The booster dose of the OAZ vaccine showed significant efficacy in preventing symptomatic infections and hospitalisation compared to the 2nd dose. Older age groups with comorbidities (particularly diabetes and hypertension), females and those at higher risk for SARS-CoV-2 exposure are more likely to have symptomatic infection after the 2nd dose. Additionally, a history of COVID-19 after the 2nd dose and CKD are associated with a higher likelihood of symptomatic infection after the 3rd dose. Investigations into the adverse effects of the vaccine after the 2nd and 3rd doses showed that the OAZ vaccine is safe. However, further studies involving larger populations and more accurate testing are needed to generalize these results.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Awareness and knowledge of drug--drug and food-drug interactions among adults in Poland – a questionnaire-based survey

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Abstract

Background: Drug-drug and food-drug interactions can affect the pharmacokinetic and pharmacodynamic properties of drugs, significantly impacting their efficiency and safety profile. Patient awareness of these interactions is vital for their ability to avoid potential risks. **Material and methods:** A total of 127 patients participated in the study and completed the questionnaire designed to assess their awareness of drug-drug and food-drug interactions, as well as their habits of medicine administration and the sources of information they relied on regarding drug usage. **Results:** Factors such as young age, female sex, higher education and urban living were linked to a greater awareness of drug-drug and food-drug interactions. Most patients reported using water to swallow pills, while some admitted to using tea or juice. Tea consumption was more prevalent among men and elderly individuals. Moreover, a higher level of education was associated with a decreased likelihood of patient consuming tea with prescribed medicines. **Conclusions:** Effective education regarding drug-drug and food-drug interactions is essential to increase patients' awareness and mitigate the potential consequences of these interactions. Initiating education on safe pharmacotherapy at the primary school level and emphasizing its significance in the training of future pharmacists and doctors is imperative.

Keywords: drug-drug interactions · food-drug interactions · patients' awareness · safety of pharmacotherapy

Citation

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Introduction

Proper administration of medications is crucial for ensuring their effectiveness and safety in therapy. One critical aspect of drug usage is the potential for interactions. Drug-drug or drug-food interactions can significantly change the pharmacokinetic and pharmacodynamic properties of medications, potentially leading to reduced efficacy or increased adverse effects [1-2]. These interactions are relatively common, for instance 166 drug-drug interactions among 76 patients were identified in a study from Crete, with 12% of these interactions classified as serious [3]. The drugs most frequently associated with these interactions include anti-bacterial and antiretroviral agents. Additionally, over-the-counter medications are often involved in such interactions, particularly non-steroidal anti-inflammatory drugs (NSAIDs), antacids, proton pump inhibitors and diet supplements [4]. In addition to interactions with other drugs medications can also interact with food or specific food components, thus changing the effectiveness of therapy by either enhancing or diminishing the drug's action, e.g. by reducing drug bioavailability of altering drug metabolism [5-7]. Therefore, it is important to avoid combining certain drugs with particular foods [8].

Drugs, particularly solid formulations (tablets and capsules) and liquid formulations (syrups and elixirs) should never be swallowed without water. Undoubtedly, water is essential for taking medications safely and effectively. Using tea or juice to swallow drugs can alter drug's bioavailability or onset of action. For instance, catechin found in green tea inhibits the CYP3A4 enzyme, which changes the metabolism of sildenafil, potentially leading to dangerous adverse effects (e.g. hypotension, priapism) [9]. Additionally, animal studies showed that green tea extract can exacerbate hepatotoxicity when administered after paracetamol [10]. Mixing drugs with fruit juices can also result in potentially harmful interactions. Grapefruit juice, well-known inhibitor of the CYP3A4 enzyme, can interact with at least 20 different drugs, e.g. terfenadine, saquinavir, cyclosporin, midazolam, triazolam and verapamil [11]. Apple can decrease the bioavailability of fexofenadine, atenolol and aliskiren, while orange juice can decrease the bioavailability of aliskiren, atenolol, celiprolol, montelukast, fluoroquinolones and alendronate. On the other hand, orange juice can enhance the bioavailability of aluminium-containing antacids [12]. Moreover, orange juice contains vitamin C, therefore it can improve the absorption of iron, which can be beneficial for patients with iron deficiency [12].

Food can also influence drug's bioavailability and in most cases it is reduced after meals [5]. For example, it was demonstrated that food intake delayed the absorption rate and decreased the bioavailability of levocetirizine [13]. Similarly, the bioavailability of esomeprazole was reduced when taken with food compared to when taken on an empty stomach [14]. Whereas, food can also enhance the drug's bioavailability, as seen with propranolol [15]. Additionally, the presence of food can delay the onset of action of certain drugs, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), which can be crucial when the rapid relief is needed [16]. Rarely food can expedite the onset of action of certain drugs, e.g. theophylline or griseofulvin taken with a high fat meal.

It is evident that understanding the potential drug-drug and food-drug interactions is essential to avoid adverse effects. Patients should be informed about the possibility of such interactions before starting a new medication regimen. The aim of this study was to assess the patients' awareness and knowledge of drug-drug and drug-food interactions that may occur during drug therapy. In addition, we investigated the medications taken by patients and their administration habits.

Materials and methods

Study design

We conducted a qualitative questionnaire-based, cross-sectional survey among adult patients from a public outpatient clinic during a consultation with a dietitian (as part of diabetes prevention) in the Pomeranian region (Northern part of Poland). Approval for the study was obtained from the Ethical Committee of the Medical University of Gdańsk (approval number NKBBN/316/2021) and all participants provided written consent to participate. Data collection took place between November 2021 and January 2023.

The questionnaire

The research tool utilized was an original questionnaire developed by the researchers from the Medical University of Gdańsk (Poland). Professionals with expertise in pharmacology reviewed the questionnaire and based on their suggestions, it was revised to its final version. The questionnaire included inquiries about their medications and related habits. It consisted of 3 parts and a total of 34 questions. Most of the questions were close-ended predefined (answer options such as 'Yes', 'No', 'I don't know'), however the participants also had the opportunity to select 'Other' or write their own answers.

The first part of the questionnaire (15 questions) aimed at gathering information about the respondents' characteristics, e.g. age, sex, place of residence (urban, suburban, rural), educational background, chronic diseases. Participants were also asked about their use of medication (on a regular and occasional basis), including any over-the-counter (OTC)

drugs or dietary supplements. Furthermore, responders were queried about their basic knowledge regarding potential interactions between different drugs and between food and drugs. The second part of the questionnaire (4 questions) was intended for patients who reported taking OTC drugs and/or dietary supplements and focused on their administration (e.g. "Do you read the leaflet before use of the new drug/supplement?", "Do you follow the advice of medical staff?", "What do you drink to swallow the drug/supplement?"). The third part of the questionnaire (6 questions) concerned the use of prescribed medications (e.g. "Do you read the leaflet before use of the new drug?", "Do you follow the medical staff advices?", "What do you drink to swallow the drug?"). Additionally, this section included more specific questions for patients who took proton pump inhibitors, fibrates and levothyroxine.

The questionnaire was prepared in the national language (Polish) and presented in a clear and simple layout. Participants received instructions on how to complete it. The questionnaire was completed during a consultation with a dietitian, either independently by the patient or with the assistance of consulting dietitian. If necessary, the dietitian read the questions aloud to the participants. After completing the questionnaire, the dietitian discussed specific aspects of food-drug interactions with each patient, particularly when the patient completed the final section regarding specific medications or reported taking multiple OTC drugs and/or dietary supplements. The dietitian provided advice on how to take these medications and supplements to avoid potential interactions. Patients with limited cognitive function (e.g. with dementia) were excluded from this study. All patients participated voluntarily and did not receive any compensation for their involvement in the study.

Statistical analyses

We aimed to achieve a 90% confidence level with a 7% margin of error, thus we calculated that the sample size should be 139 respondents. The questionnaires were collected by a single researcher within a limited timeframe, therefore such sample size provided a balance between statistical validity and practical feasibility. Pearson's chi-squared test and descriptive statistics were applied to the data. The Chi square test was employed to examine correlations between the knowledge of interactions, dietary supplement use and sex, age, level of education and the presence of chronic diseases. All statistical analyses were performed using the Statistica software version 10 (TIBCO Software Inc, Palo Alto, USA)

Results

Study population

A total of 127 patients agreed to participate and complete the questionnaire. The majority of participants were female (71.7%, n = 91), with the highest proportion within the 41-50 years of age range (36.2%, n = 46). Furthermore, more than half of the participants had higher education (51.2%, n = 65) and a notable 29% (n = 37) had a medical background, they were either graduates or current students of medical universities. Additional demographic details are provided in Table 1.

Table 1. Background characteristics of respondents

Parameter under study	Participants (n = 127)
Sex:	
Female	91 (71.7%)
Male	36 (28.3%)
Female/male ratio	2.5
Age groups of participants [years]:	
18-28	37 (29.1%)
29-40	25 (19.7%)
41-56	46 (36.2%)
> 56	19 (15.0%)
Educational level:	
Elementary	11 (8.7%)
Secondary	51 (40.1%)
Higher	65 (51.2%)
Medical background:	
Yes	37 (29.1%)
No	90 (70.9%)
Place of residence:	
Village	8 (6.3%)
City with < 150000 inhabitants	74 (58.3%)
City with > 150000 inhabitants	45 (35.4%)

Drugs and diet supplements taken by the participants

Patients were asked about their chronic illnesses and the prescription medications which they take chronically (> 1 month). Among the respondents, 55% (n = 70) admitted to using prescription drugs regularly (Figure 1). Additionally, 42% of participants (n = 53) acknowledged

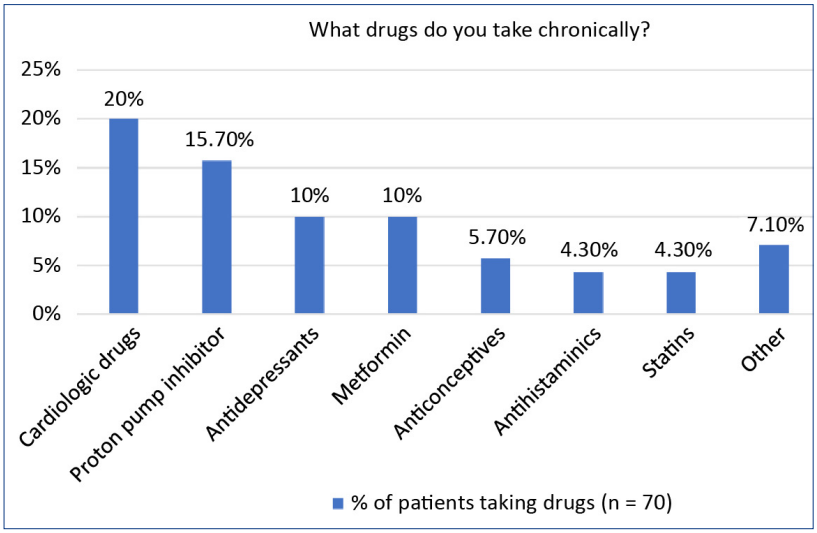

Figure 1. Most common drugs taken chronically by patients

regular use of OTC drugs and/or dietary supplements. Interestingly, OTC medication and supplement use was more prevalent among younger adults ((78% of the 18-28 years of age group), compared to the rest of the population (p = 0.00000). Moreover, women were found to use OTC drugs and/or dietary supplements more frequently than men (p = 0.00000). The most commonly used supplements included vitamin D (75.5%, n = 40), supplements for hair and nails (18.9%, n = 10) and magnesium (13.2%, n = 7). A notable correlation was observed between sex and specific supplement usage. Specifically, women were more likely than men to take vitamin D (41% versus 8%) (p = 0.00041) and supplements aimed at improving nail and hair the condition (exclusive to women) (p = 0.03824). Furthermore, younger adults aged 18-28 were more likely (70% of this group) to take vitamin D compared to other age groups.

The majority of the patients who took prescription drugs chronically (61.4%, n = 43/70) reported reading the drug leaflet (also known as summary of product characteristics or drug monograph) before use and nearly all patients (99%, n = 69/70) stated that they followed the doctor's instructions regarding medication intake. Among patients taking OTC or/and dietary supplements, 70% (n = 37/53) claimed to read the drug's leaflet before use and all of them (n = 53/53) indicated adherence to either doctor's or pharmacists' instructions. Interestingly, women (71%) were more likely than men (39%) to read the leaflets (p = 0.00073).

Drug administration

The vast majority of participants used water to swallow pills: 99% of those taking prescribed drugs (n = 69/70) and 100% of those taking OTC or/and diet supplements (n = 53/53). A small group admitted to using tea (17.1%, n = 12/70 of those taking prescribed drugs and 13.2%, n = 7/53 of those taking OTC or/and dietary supplements) or juice (5.7%, n = 4/70 of those taking prescribed drugs and 9.4%, n = 5/53 of those taking OTC or/and dietary supplements). Interestingly, men were more likely than women to drink tea while taking prescribed drugs (p = 0.01390), although there was no such correlation in the group taking OTC drugs or/and dietary supplements. Furthermore, there was no correlation between sex and drinking juice in either group. Additionally, 45.5% of people > 56 years of age admitted to drinking tea to swallow prescribed pills (p = 0.03499), compared to 13.3% in the 41-56 age group, 0%, in the 29-40 age group and 15.8% in the 18-28 age group. However, there was no such correlation in the group of patients taking OTC or/and dietary supplements. Moreover, there was no correlation between age and drinking juice in either group. Additionally, there was a correlation between the patients' level of education and their approach to prescribed drug administration. Among patients taking prescribed drugs, 85.7% of respondents with higher education exclusively used water to swallow their medications, while this figure was 81.8% for those with secondary education and only 16.7% for those with primary education (p = 0.00053). Notably, individuals with primary education were more likely to use a different beverage than water to swallow medicines (p = 0.00447). Furthermore, it was found that higher education was associated with a lower likelihood of patients drinking tea with prescribed medications (p = 0.00302).

Interestingly, 30.5% of individuals taking prescription drugs or OTC drugs or dietary supplements (n = 29/95) admitted that they sometimes they took their medication differently than recommended by their doctor or written in the leaflet. This change was primarily driven by convenience (48.3%, n = 14/29) or previous experience with taking medication (48.3%, n = 14/29). However, such behaviour was not associated with sex, age, education level or place of residence.

Knowledge about interactions

The next segment of the survey focused on participants' awareness of potential drug-drug and food-drug interactions. It was noted that age, sex, education level and place of residence could influence the patients' knowledge of these interactions (see Table 2).

Table 2. Awareness of drug-drug and drug-food interactions in selected groups of respondents

Compared parameters under study	% of respondents conscious of food--drug interactions	p (Pearson's chi-squared test)	% of respondents conscious of drug--drug interactions	p (Pearson's chi-squared test)
Sex: Female Male	 63% 33%	0.00281	 79% 64%	0.07476
Age groups of participants [years]: 18-28 29-40 41-56 > 56	 86% 44% 43% 32%	0.00005	 97% 76% 65% 53%	0.00066
Educational level: Elementary Secondary Higher	 9% 45% 69%	0.00024	 36% 61% 92%	0.00000
Healthcare background: Yes No	 100% 36%	0.00000	 100% 64%	0.00003
Place of residence: Village City with < 150000 inhabitants City with > 150000 inhabitants	 13% 42% 82%	0.00001	 13% 69% 96%	0.00000

Furthermore, among the respondents who were aware of drug-drug interactions, 72% were also knowledgeable about the potential interactions between drugs and food (p = 0.00000). Interestingly, larger proportions of participants were aware of possible drug-drug interactions compared to interactions between drugs and food (74.8%, n = 95 vs. 54.3%, n = 69). The use of drugs and dietary supplements regularly could enhance the patients' awareness of both drug-drug and food-drug interactions. For more detailed information, please refer to Table 3.

Interestingly, only 7% of the participants who were aware of potential drug-food interactions, admitted to drinking tea while taking pills, compared to 43% in the group lacking this knowledge (p = 0.00000). Additionally, a significant difference was observed in the use of juice with drugs between those who were aware and unaware of drug-food interactions (p = 0.00033), specifically, only 3% of individuals who were aware of the drug-food interactions drank juice with their medication.

Discussion

The primary objective of this study was to evaluate patients' awareness of potential drug-drug and food-drug interactions. We discovered that such awareness is associated with various demographic factors including age, sex, education level, place of residence and the use of different medications and dietary supplements. In our study 55% of the participants reported taking prescription drugs on a chronic basis and 42% of them claimed taking OTC drugs or/and dietary supplements. The most commonly used medications were cardiovascular drugs (statins and beta-blockers) and proton pump inhibitors, both of which are associated with numerous potential interactions [17].

Interestingly, we found that OTC drug or/and dietary supplement use was more prevalent among the youngest participants (18-28 years of aged). Moreover, a significant majority (70%) of this age group reported taking vitamin D, which was notably more common than in other age groups. Additionally, OTC drugs and/or dietary supplements were more commonly

Table 3. Awareness of drug-drug and drug-food interactions in groups of respondents using various drugs and dietary supplements

Compared parameters under study	% of respondents conscious of food--drug interactions	p (Pearson's chi-squared test)	% of respondents conscious of drug--drug interactions	p (Pearson's chi-squared test)
Chronic usage of prescribed drugs: Yes No	 74% 30%	0.00000	 94% 51%	0.00000
Usage OTC drugs and diet supplements: Yes No	 74% 40%	0.00017	 87% 67%	0.01139
Taking Vitamin D: Yes No	 85% 40%	0.00000	 93% 67%	0.00184
Taking Levothyroxine: Yes No	 88% 49%	0.00000	 100% 64%	0.00003

used by women compared to men, mirroring findings of Burnett et al. In their study involving 4895 volunteers in Australia, by 47% of women used supplements, compared to 34% of men [18]. Contrary to our observations, the use of dietary supplements was found to be higher among older individuals and those with higher levels of education [18]. A study conducted in China revealed that only 0.71% of population > 6 years of age admitted to using a dietary supplement [19]. Similarly to the findings of Burnett et al., the prevalence of supplement intake correlated with age and educational level of participants [18]. Interestingly, in our study there we did not observe any statistically significant correlation between the use of OTC drugs and/or dietary supplements and the level of education. A study conducted among medical students in India found that 45.3% of participants (notably more females than males) consumed multivitamin supplements [20]. Similarly, in our study women were more inclined to use supplements for nail and hair health as well as vitamin D. This heightened usage of nail and hair supplements seems to be in line with the common perception that women tend to be more concerned about their appearance than men. The vitamin D supplementation could be linked to the widely announced recommendations for its use in prevention of osteoporosis, a condition more prevalent among women [21].

It is typically the responsibility of the prescribing physician to provide the patients not only with dosage instructions but also to advise on the timing of administration in relation to meals and take into account potential interactions with food and beverages. In our study nearly all (99%) patients who reported taking prescription drugs chronically also stated that they adhered to their doctor's instructions regarding medication administration. When it comes to OTC drugs or dietary supplements, pharmacist may play a crucial role in clarifying the above-mentioned matters and discussing potential interactions. In our study cohort of patients taking OTC drugs and/or dietary supplements, all participants indicated that they followed the instructions provided by doctors or pharmacists for medication intake. However, some studies highlighted the inadequate knowledge about drug-drug and drug-food interactions among health care providers. For instance, in the United States, only 18.2% of the 950 surveyed prescribers were able to identify the pairs of drugs that should not be used together [22]. Therefore, it is plausible that information about drug interactions is not consistently conveyed to patients.

In addition to following the instructions provided by a physician or pharmacist, it is important for patients to read the leaflet included with their medication. The information in these leaflets (e.g. details about proper drug administration, correct dosages, contraindications and potential interactions with other drugs or certain foods) should be clear and easy to understand [23]. In our study, the majority of the patients taking prescribed drugs (61.4%) and those using OTC drugs or/and dietary supplements (70%) reported reading the leaflet before starting new medication. Our findings align closely with those reported by Nathan et al. that 70.4% of patients in New York City acknowledged reading a leaflet before using of the new drug (49.2% marked that they "always" read and 21.2% marked "often"). Additionally, 98.8% of patients

claimed that reading the leaflet was “very” or “somewhat” useful [24]. In contrast, researchers from Lebanon noted that 61.2% of patients admitted to not reading the leaflets before using drugs [25]. These discrepancies may arise from the fact that in our study we asked patients about reading drug’s leaflets in general, rather than specifically focusing on the leaflets about new drugs. Interestingly, in our study women (71%) were more likely than men (39%) to read the leaflets. However, we did not find any other reports about the correlation between sex and leaflet reading.

We observed that men and particularly more often elderly people drank tea while taking prescribed medications. This can be attributed to the fact that in Poland tea is generally a more popular beverage among the older generation. It is noteworthy that black tea contains caffeine and can potentially interact with many drugs, e.g. psychiatric medications, antiarrhythmics, bronchodilators and antibiotics [26]. These interactions occur because caffeine is metabolised by the same enzyme (cytochrome P450 1A2) as many drugs. Similarly, green tea can interact with drugs such as statins, beta-blockers, warfarin or sildenafil [9]. Therefore, patients should be informed about the potential interactions between drugs and beverages such as coffee, tea or juice. Our study revealed that individuals with higher education levels were less likely to drink tea with prescribed medicines. This highlights the need to educate patients about drug-beverage interactions to avoid adverse effects.

We observed that women, younger adults (aged 18-28), individuals with higher education level and those residing in urban areas exhibited greater awareness of potential drug-drug and food-drug interactions. Moreover, awareness regarding drug interactions, both with other medications and with food, was higher among the patients who chronically took medications, regardless if these were prescribed (particularly levothyroxine), OTC drugs or dietary supplements (particularly vitamin D). Additionally, participants with background in healthcare (e.g. healthcare workers or medical university students) demonstrated greater awareness of drug-drug and food-drug interactions, which may be attributed to their basic knowledge of biochemistry and pharmacology.

Indeed, enhancing patient knowledge about medications can significantly improve treatment compliance. In our study, we found than only 7% of individuals aware of potential drug-food interactions consumed tea while swallowing pills, compared to 43% of those who were unaware of such interactions. This underscores the importance of educating patients about potential interactions in order to mitigate the risk of adverse effects. Numerous studies in the literature support the positive impact of patient education on medication management. For instance, Detry-Morel reported that improved efforts to inform patients with open-angle glaucoma or ocular hypertension led to better compliance and persistence with therapy resulting in fewer medication errors and improved efficacy [27]. Similarly, Micheli et al. concluded that patients with better understanding of why they were taking a particular medication were less likely to discontinue treatment [28]. Kristensson et al. highlighted the critical importance of informing patients about their prescribed medications, even in acute care settings [29]. Furthermore, it is essential that the information provided to patients is clear and understandable. Gustafsson et al. found that while most information was well understood by patients, the sections concerning ‘risks of interactions’ and ‘contraindications’ were challenging, particularly for the elderly patients [30]. This underscores the fact that in order to mitigate the risk of interactions, patients must have a comprehensive understanding of their medications. First, patients must be aware that such interactions are possible, which empowers them to inquire about this with their physicians and consequently, they can actively participate in their own healthcare decisions. However, a study from Lebanon revealed that 38.7% of participants did not regularly discuss their medications with physicians and 53.9% did not enquire about potential interactions with pharmacist. In our research, a better understanding of both drug-drug and food-drug interactions was associated with female sex, higher education, medical background and chronic medication use. These findings are consistent with the survey conducted in Saudi Arabia, which reported the participants’ knowledge of food-drug interactions as moderate, with higher knowledge linked to female sex, healthcare-related occupations with and the presence of chronic disease [31]. Similarly, in a study conducted in South Africa, only 30-50% of patients were able to identify potential food-drug interactions [32]. The patients in that study had a secondary or lower level of education, which aligns with our findings, where only 45% of respondents with secondary education and 9% of those with elementary education were aware of food-drug interactions.

Our study has some limitations. The study group was relatively small and homogenous (participants come from only one region of one country). Moreover, some patients missed their appointments, resulting in a smaller number of participants and completed questionnaires than we intended (based on our calculations of optimal sample size). Additionally, as with most questionnaire-based studies, there is a risk that respondents provided answers based on what they believed to be correct rather than on their true knowledge. To obtain more representative data and a deeper understanding of public’s knowledge about this subject, it would be beneficial to conduct similar surveys across various regions with more detailed questions. Furthermore, longitudinal studies that include consultations on food-drug interactions could help track changes in awareness and behaviour over time, as well as evaluate the effectiveness of patient education.

Conclusion

Our study revealed a moderate level of awareness regarding drug-drug and food-drug interactions among Polish adults, with notable correlations observed with sex, educational level and chronic medication usage. It is worth to emphasise the role of patients' education as the best way to enhance the awareness of drug interactions and to mitigate potential health risks associated with improper medication use. Introducing basic knowledge about medication usage into primary and secondary school curricula could help to educate future adults, while medical university students should receive more comprehensive training on this topic. Furthermore, eHealth platforms and applications could be introduced to improve both the awareness and knowledge about potential drug interactions [33].

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Conflicts of interest

The authors declare that no conflicts of interest exist.

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None.

Availability of data and materials

The corresponding author is committed to share collected data upon request. All data are anonymized to respect the privacy of patients who participated in this study.

Supplementary materials

The questionnaire developed for this study (in Polish language).

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RESEARCH ARTICLE

Improving workflow at the Emergency Department – simple lessons from the lean management concepts

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Abstract

Background: Work in the hospital emergency department (ED) is characterized by a significant (and sometimes excessive) number of patients in relation to medical staff and space and high variability of clinical situations, all in conditions of time deficit. The concept of lean management (LM) may be helpful in solving some of the organizational problems at the ED. One of the tools derived from LM is the 5S method (sort, set in order, shine, standardize and sustain), which serves to organize the workflow, eliminate waste and increase patient safety. **Material and methods:** In the ED of University Clinical Hospital in Opole (Poland) we used survey methods (questionnaires, direct interviews and group discussions with the participants) to identify the issues that caused the greatest difficulties in the work flow. 3 months after implementing changes, we conducted a survey among the participating ED nurses and paramedics to obtain opinions on the introduced changes. **Results:** Majority of the participants found the implemented changes (e.g. equipment checklists, standardized equipment and supply placement in all ED areas) ”definitely necessary” and ”rather necessary.” **Conclusions:** The implementation of LM, particularly the 5S method and checklists, seems to be useful in the organization of work in the ED and was positively assessed by the staff.

Keywords: management · emergency department · checklist · lean healthcare · implementing change

Citation

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Introduction

The hospital emergency department (ED) operates 24-hours non-stop and is one of the key elements of the healthcare system. The literature from recent years shows that EDs fill the gaps in healthcare systems around the world by acting as a buffer for patients who do not have a health emergency and for various reasons do not use primary healthcare services at outpatient clinics [1-3].

Due to the above, overcrowding (an excessive number of patients in relation to the staff and space resources) is observed at many EDs around the world [4]. Admitting to the ED patients without severe illness significantly prolongs several processes (e.g. admission and initial stabilization of the patient, diagnostics), burdens the department's resources and reduces the efficiency of the hospital staff [5]. The boarding of patients (i.e. hospitalizing in the ED patients who are *de facto* admitted to other hospital departments) significantly extends the ED patient's length of stay (LOS), causes additional difficulties in the workflow of the ED staff and has been shown to increase in-hospital mortality [6-7].

Solving the above-mentioned problems undoubtedly would require joint effort of healthcare managers (hospital and outpatient clinic managers) together with regional and national health policymakers. In the meantime, it is reasonable to search for tools and solutions at the micro-level, one ED at a time. The literature suggests that some of the difficulties in the ED workflow may be reduced by implementing specific management concepts and tools. Lean healthcare (LH) is a branch of the lean management (LM) concept and together with the 5S method originates from the Japanese industrial sector [8-9]. 5S is an abbreviation of the processes aimed at optimizing the use of equipment and work space: *seiri* (sort), *seiton* (set in order), *seiso* (shine), *seiketsu* (standardize) and *shitsuke* (self-discipline). Sometimes a 6th element (safety) is added to the 5S method in the literature, i.e. ensuring the safety of the work environment by identifying potential places that threaten the safety of employees and eliminating them. The methods for this include employee training and using visual management tools, e.g. painting a trace/arc of an opening door on the floor of a busy corridor.

Another aim of the LH concept is the complete elimination of *muda* (waste), defined as all activities that are not related to patient care/treatment or ending the patient's stay in the hospital [8-10]. Examples of waste in the ED include the extended LOS resulting from repeated activities (e.g. transporting the same patient several times between the ED and the radiology unit), defective (or missing) equipment and the so-called "bottlenecks" (e.g. waiting for medical triage, waiting for transport to the radiology unit) [11-12]. Authors point that eliminating such types of waste improves the efficiency of staff, increases the patient flow through the ED, thus reducing the overcrowding and costs, while improving the safety and quality of care [12]. However, the complexity of processes/tasks, resistance to change and lack of standardization are barriers to the implementation of the LH concept in the ED [13]. Therefore, the implementation of LH requires full support of the management staff and medical staff in identifying and eliminating waste, e.g. using data analysis or value stream mapping (a graphic presentation of the stages of the particular process).

Besides 5S, another simple and low-cost tool for optimizing work in the ED are checklists. They can be used as part of the assessment of the availability and function of equipment at the particular area and identifying threats resulting from its deficiencies or defects [14-15]. Checklists allow the employee to quickly detect missing pieces of equipment of individual pieces of equipment through verification and identification by marking individual points [16]. However, it should be remembered that despite low financial costs and the ease of use, their implementation and effectiveness strongly depend on the awareness and motivation of the medical and management staff at every level [17].

Our goal was to implement several solutions derived from LH in the ED of a university hospital. We then analyzed the feedback of the ED nurses and paramedics regarding their satisfaction with the resulting changes in their tasks and in the functioning of their department.

Material and methods

This study was conducted in 2022-2023 in the ED of the University Clinical Hospital (UCH) in Opole (Poland) after obtaining the approval of the hospital Management staff. Bioethics Committee approval was not necessary because this study did not meet the criteria of a medical experiment. The UCH is a public, academic hospital, trauma center (pediatric and adult) as well as the largest hospital in the Opole voivodeship (province). The patient flow at the UCH ED is approximately 150-180 patients per day (approximately 3500-4000 patients per month), which is in the average among EDs in Poland. Nurses and paramedics work 12-hour shifts at the ED. A total of 17 nurses and 16 paramedics participated in this study and voluntarily completed the survey questionnaires. In this study we decided to analyze the workstations and workflow of ED nurses and paramedics only, therefore the ED physicians did not participate.

This study consisted of 3 stages. First, we used survey methods (questionnaires, direct interviews and group discussions with the participants) to identify the issues that caused the greatest difficulties in the work flow. The 2nd stage of the study included interventions: the use of the 5S method and checklists in cooperation with the participants. Three months

later (3rd stage) we used an original survey questionnaire to collect feedback from the participants regarding the effectiveness of the introduced changes (Figure 1). This was a pilot study, therefore a 3-month observation was chosen.

The ED was divided into 6 areas (registration, medical triage, surgical, resuscitation, observation and pediatric) and an "area supervisor" was selected for each area. In addition, 2 appointed "leaders of change" cooperated with the "area supervisors" and monitored the implementation of the 5S method during their shifts in the ED. Although every employee was responsible for implementing 5S in the areas, the "area supervisors" together with the "leaders of change" carried out rounds in accordance with the agreed-upon schedule and checklist of what to check.

The survey questionnaire (developed by the first author) consisted of 31 single-choice closed questions regarding sociodemographic data, job satisfaction, job involvement and organization of work. In this study we analyzed only questions regarding work organization. Returning a completed questionnaire was equivalent to expressing consent to participate in the study.

Data analysis from the survey was performed in R, version 4.2.1 (open-source). Analysis of quantitative variables was performed by calculating the mean, standard deviation, median and quartiles. Analysis of qualitative variables was performed by calculating the number and percentage of occurrences of each value. Comparison of qualitative variable values in groups was performed using the chi-square test (with Yates' correction for 2 x 2 tables) or Fisher's exact test where low expected frequencies appeared in the tables. Comparison of quantitative variable values in 2 groups was performed using the Mann-Whitney test. Comparison of quantitative variable values in ≥ 3 groups was performed using the Kruskal-Wallis test. After detecting statistically significant differences, post-hoc analysis was performed using Dunn's test to identify groups that differed statistically significantly. All p values < 0.05 were interpreted as statistically significant.

Results

Interventions undertaken

Based on direct interviews with staff, we compiled a list of problems that cause difficulties and waste in everyday work at the ED. The main problems included: shortages of equipment in particular areas and the lack of marking of faulty devices. Interventions were undertaken to eliminate or reduce the number of these problems, which consisted of using the 5S method, visual management, checklists and equipment lists in all areas of our ED (Table 1).

At the registration desk, the countertops and document cabinets were decluttered using the 5S method. A key panel was installed to make access to keys (and searching for them) easier (Figure 2). Each key was attached to a color-coded key chain: red (keys to rooms in the resuscitation area), green (registration and medical segregation area), blue (isolation area), yellow (observation area), black (staff rooms). A paper list of rooms and their assigned key numbers was placed under the key panel to further ease searching for them.

Paper checklists for each ED area were prepared in the form of a table with a list of equipment that should be found in that particular area (Figure 3). The staff recorded the following items: missing piece of equipment at the workstation, equipment malfunction, equipment sent to service, incomplete equipment. The aim was to increase control over the equipment and ensure its efficient function, which is crucial when treating acutely ill patients. After 1 month, the implementation of changes so far was summarized during a department-wide meeting and the staff was asked for verbal feed-

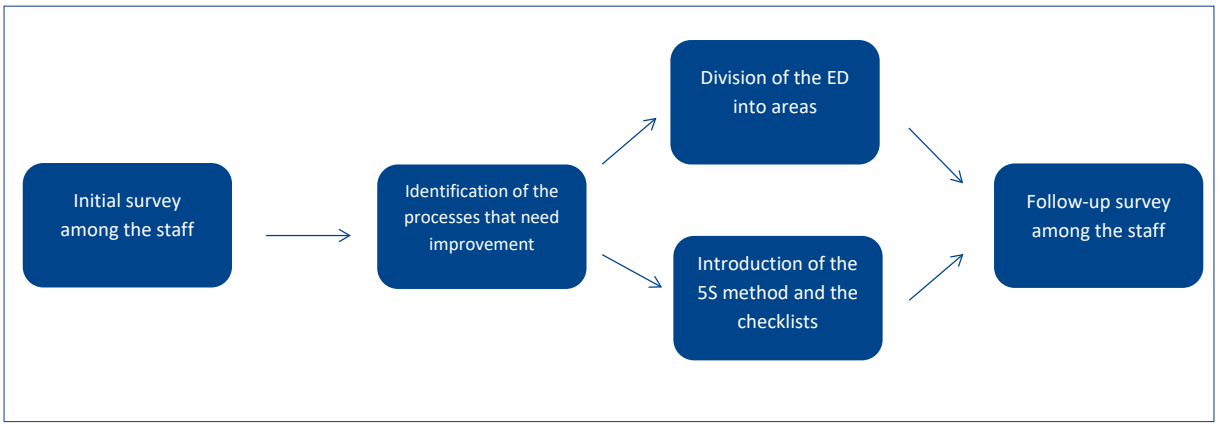


Figure 1. Implementation of LM methods at our Emergency Department

Table 1. Actions taken the ED of the UCH in Opole as part of the 5S method

Step of the 5S method	Actions taken in the ED
seiri (sort)	Equipment that was not used in everyday work was moved to storage.
	Equipment that was of uncertain usefulness was placed in a box marked with a red label along with that day's date. After storing for 30 days, a decision was made to either keep that equipment in storage or to return it to the work environment.
seiton (set in order)	Using visual elements (e.g. symbols, labels) to mark where equipment is stored, enabling quick finding and putting it back in the same place.
	All medications were placed in cabinets (and in the refrigerator) in accordance with the applicable hospital procedure.
	Equipment was arranged according to the frequency of its use.
seiso (shine)	Developing rules (e.g. regarding maintaining cleanliness/order at workstations, periodic equipment inspections).
	Spreading awareness that the above activities are part of every employee's daily tasks.
seiketsu (standardize)	Developing a checklist for equipment for each area.
	Standardization of equipment in the cabinets, drawers and resuscitation carts in each of the ED areas.
	Creating equipment lists along with its location in each cabinet and drawer.
shitsuke (sustain)	Conducting internal audits according to a developed checklist.

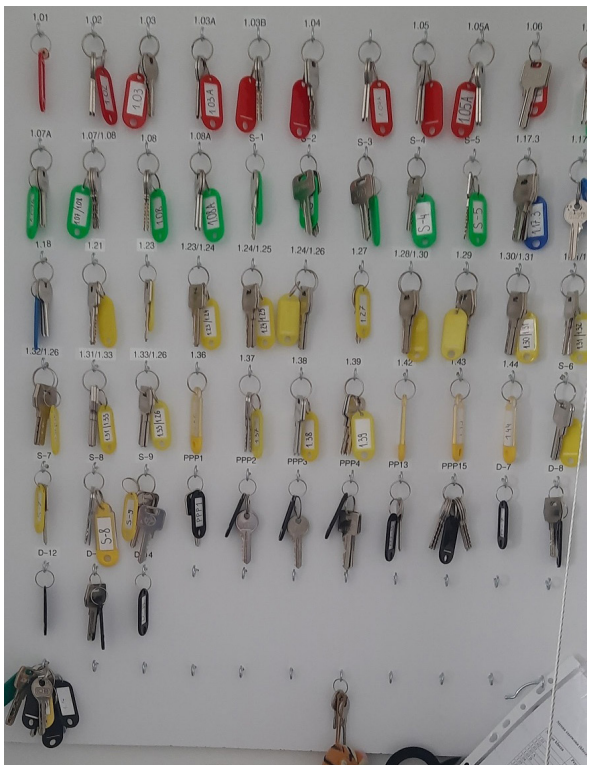


Figure 2. Example of applying the 5S method at the registration desk

back and suggestions for further improvements. Duplicates of the same equipment in several rooms were eliminated and errors in the names of some equipment were removed. The checklists were not filled-out completely, which resulted in lower quality of care and less patient safety (e.g. due to not checking the defibrillator battery charge level). In order to solve the problem of incomplete checklists, we removed the detailed lists of parts each of each piece of equipment and left only the particular device name. As a result, the checklists were significantly shortened, use of paper was reduced and the checklist completion has increased.

For each ED area we created lists of equipment, specifying its exact location in the cabinets and drawers (Figure 4). Such standardization of workstations made it easier to monitor the use of/shortages of supplies and to train new employees. These lists were located in the same place in each room: on the inside of the door to the cabinet where infusion fluids were stored.

Using visual management, all equipment storage spaces (drawers, cabinets, resuscitation carts) were clearly labeled by placing stickers with a description of the content (Figure 5). Paper documentation was organized in such a way that all the most-frequently used document templates were in one place

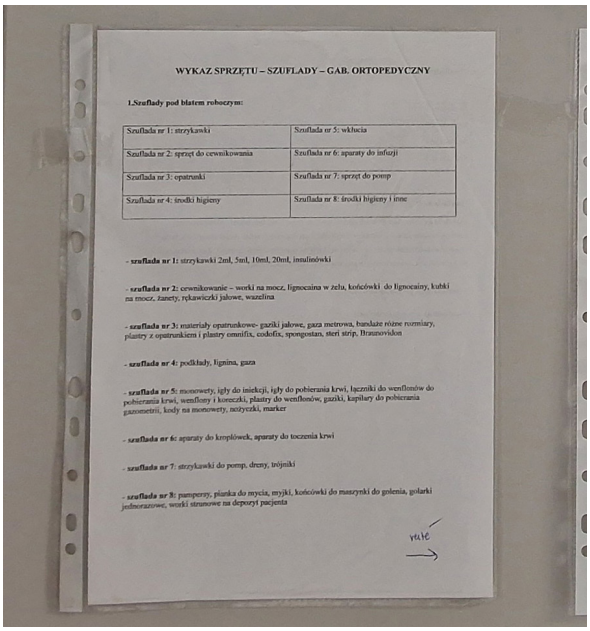
ROOM 7

Y – It is complete and fully functional,
N – Not here, malfunctioning, incomplete
* – Near the equipment there is a detailed list of all the parts that must be checked

Month ..... Year .....

Equipment/Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	39	31
	Is the equipment ready to use? **Y/N**																														
*** Patient monitor** MINDRAY BENEVISION N12																															
Thermometer MEDISANA																															
5 wheelchairs																															
NOTES																															

Figure 3. Example of a checklist


WYKAZ SPRZĘTU – SZUFLADY – GAB. ORTOPEDYCZNY

1.Szuflady pod blatem roboczym:

Szuflada nr 1: strzykawki	Szuflada nr 5: wkłucia
Szuflada nr 2: sprzęt do cewnikowania	Szuflada nr 6: aparaty do infuzji
Szuflada nr 3: opatrunki	Szuflada nr 7: sprzęt do pomp
Szuflada nr 4: środki higieny	Szuflada nr 8: środki higieny i inne

- **szuflada nr 1:** strzykawki 2ml, 5ml, 10ml, 20ml, insulinówki

- **szuflada nr 2:** cewnikowanie – worki na mocz, lignocaina w żelu, końcówki do lignocainy, kubki na mocz, zaręty, rękawiczki jałowe, wazelina

- **szuflada nr 3:** materiały opatrunkowe- gaziki jałowe, gaza metrowa, bandaże różne rozmiary, plastry z opatrunkiem i plastry omnifix, codofix, spongostan, steri strip, Braunovidon

- **szuflada nr 4:** podkłady, lignina, gaza

- **szuflada nr 5:** motowety, igły do iniekcji, igły do pobierania krwi, łączniki do wenflonów do pobierania krwi, wenflony i koreczki, plastry do wenflonów, gaziki, kapilary do pobierania gazometrii, kody na motowety, nożyczki, marker

- **szuflada nr 6:** aparaty do kroplówek, aparaty do toczenia krwi

- **szuflada nr 7:** strzykawki do pomp, dreny, trójniki

- **szuflada nr 8:** pampersy, pianka do mycia, myjki, końcówki do maszynki do golenia, gołarki jednorazowe, worki strunowe na depozyt pacjenta

Figure 4. Equipment list

Figure 5. Example of visual management

and were described in such a way that it was visible if any were missing (Figure 6).

Survey study

The assessment of the changes introduced by the nurses and paramedics of our ED was verified using surveys. Nurses constituted 51.51% (n = 17) of the respondents, and the paramedics 48.48% (n = 16). The most frequently marked suggestion regarding the functioning of the department by the staff was the "need for more training", indicated by 88.24% (15) nurses and all paramedics. During the discussion in groups, the training needs were specified (e.g. medical triage according to the Emergency Severity Index algorithm, interpretation of ECG and management of selected arrhythmias, interpretation of arterial blood gas tests, LM concept and 5S method).

Providing/receiving information on the equipment in the room during each shift was considered "definitely necessary" by 35.29% (6) of nurses and 43.75% (7) of paramedics. It was considered "rather necessary" by 41.18% (7) of nursing staff and 43.75% (7). In both professional groups, nobody considered it "definitely unnecessary". No significant differences were found between professional groups (p = 1).

Providing/receiving information on the status of disposable equipment and medicines in the particular ED area during each shift was considered "definitely necessary" by 35.29% (6) of nurses and 37.50% (6) of paramedics. It was considered "rather necessary" by 52.94% (9) of nursing staff and 43.75% (7) of paramedics. It was not described as "definitely unnecessary" in any of the groups. There were no significant differences between professional groups (p = 0.647).

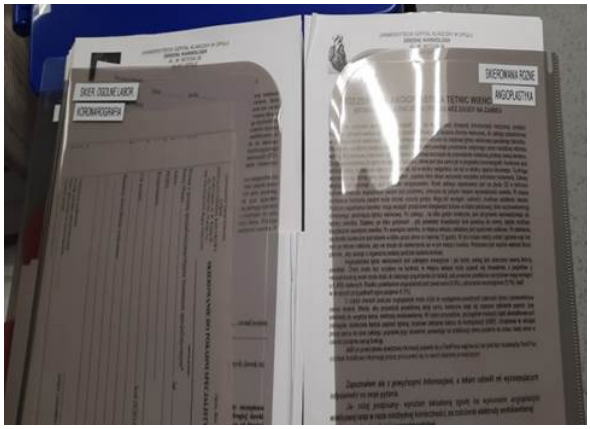


Figure 6. Organizing the paper documentation

Descriptions of the equipment arrangement in each drawer and cabinet were considered "definitely necessary" by 35.29% (6) of nurses and 62.50% (10) of paramedics, whereas 35.29% (6) of nurses and 25% (4) of paramedics considered them "rather necessary". There descriptions were considered "rather unnecessary" by 17.65% (3) of nursing staff and 6.25% (1) of paramedics. None of the respondents considered them "definitely unnecessary". No significant differences were found between professional groups ($p > 0.499$).

Discussion

The literature suggests that the organizational changes that are necessary to implement in the ED include, among others, medical triage training, proper allocation of staff in individual areas, designating a nurse- coordinator on each shift, improvements in the transfer of patients to other hospital departments. The above-mentioned changes increase the level of patient and staff safety [18]. Many management concepts implemented in healthcare facilities (quality management, risk management, process management and human resources management) can lead to increased efficiency, shortened waiting times for a particular service and improved quality of provided healthcare services [19-23]. The LM concept has gained considerable popularity in the recent years [24-27]. The implementation of LM seems to be necessary particularly in the ED, because its ineffective management may affect the functioning of other hospital units [28-29]. In our study, the majority of the participants considered the implemented changes beneficial and necessary.

The benefits of implementation of LM are described most broadly in the context of American hospitals, where it was demonstrated, among other things, that by changing the equipment setup and developing standard work methods, it is possible to shorten the average time of processing histopathological test results from 4 to 3 days, prepare 30% more results and reduce the number of errors in the results of processed diagnostic tests [10]. Verbano et al. indicated that thanks to the implementation of LM in the ED, it is possible to reduce the waiting time for radiological test results, which is valuable for both patients and doctors [30].

Thanks to the introduction of changes related to LM, the waiting time of patients at individual stages of their stay in the ED may be shortened, e.g. the waiting time for triage may be shortened from 3.18 minutes to 2.63 minutes; for the first contact with a doctor from 13.68 minutes to 11.65 minutes, and the total stay from 157.70 minutes to 117.71 minutes [31]. Even such minor changes seem significant, considering that the average LOS in the ED is about 258 minutes, of which 80% are spent on activities that do not provide value from the patient's point of view (e.g. waiting for diagnostic test results, waiting for a specialist's consultation, waiting for discharge report). The shortening of the total stay as a result of implementing LM is also noted the literature review by Tlapa et al., showing that it may be shortened by up to 142 minutes [32]. One of the changes may be the use of visual management to mark paths and rooms in the ED, which reduces the time triage staff must spend explaining the patient's way to a given area [33]. Other researchers also point to the benefits of implementing LM in terms of speeding up the flow of patients through the ED [31, 34-35]. In our study, we also used visual management tools (stickers describing the contents of each cabinet and drawer, Figure 5).

The LM concept can help eliminate waste in the ED, such as the duplication of information in paper forms/record books and in the computer system. Another example is organizing the medicines by simply dividing them into 3 groups and marking them with colors (e.g. green – used in large quantities, yellow – used irregularly, red – used exceptionally rarely), adjusting their orders to the actual demand [36]. Similarly, in our study we standardized the way all medications were ordered in each cabinet and refrigerator), so that the staff spend less time searching for them or checking their quantities. Furthermore, we sorted all pieces of equipment and removed to storage those which were not used in daily work or were of uncertain usefulness (Table 1).

By combining the LeanSixSigma concept (a quality improvement method that identifies problems before they occur) in the EDs of 3 hospitals in Florida (USA), the overall LOS indicator was improved by 22-26%, which increased patient satisfaction from the 61st percentile to > 90th, with simultaneous savings of $4-7 million. This was achieved by streamlining the triage process, reorganizing the medical triage area, standardizing procedures by introducing clinical guidelines into everyday practice (mainly regarding the method of performing specific medical procedures) and eliminating the so-called "bottlenecks" [37]. Although we were not able to ana-

lyze specific time-related data, in our study we eliminated one potential bottleneck (time wasted on searching for keys) by creating a key panel and labeling each key with a color-coded key chain (Figure 2).

Alowad et al. presented a holistic approach to optimizing the work of the ED. The opinions of staff and patients were taken into account, patient flow maps were developed and the so-called "bottlenecks" were identified (e.g. waiting for registration or for imaging tests). The authors showed that the reasons for the overload of the ED are, among others, in the area of management (e.g. lack of standardized documentation, inefficient system for reporting problems), in the number and experience of nursing and medical staff, in the area of quality (e.g. lack of a developed training plan, lack of a quality improvement team in the ED), in the area of patients (lack of awareness of when to report to the ED) and in the area of the department's resources. [38]. In our study we also noted lack of standardized paper documentation and organized it accordingly in all areas of our ED (Figure 6).

Barriers to implementing changes in the ED include ignoring the value that can be obtained thanks to motivated and energetic staff [37]. The feedback of medical staff on the changes being introduced may contribute, among other things, to greater motivation to undertake actions and identification with the unit. For the successful optimization of ED management, it is necessary to raise staff awareness of selected management concepts and tools through training and education, enabling employees to submit ideas for improvements and solve problems [39-41]. This correlates with our results that show that ED nurses and paramedics expect more training and is willing to participate in it.

Further research directions

There is a lack of current research on the effectiveness of management concepts (including LH) in optimizing the functioning of Polish healthcare facilities. While conducting such studies it would be important to take into account the impact of this implementation on the patient's LOS at all stages and on the total stay in the ED. It would also be important to identify the processes taking place in the ED, visualize them and identify the so-called "bottlenecks", which would directly affect their improvement, which is crucial in the conditions prevailing in the ED.

Limitations

The main limitation of this study is the lack of data on the patient's LOS in the ED at its individual stages (e.g. time to triage, time to first contact with a doctor, time from ordering tests to results, etc.) and the overall LOS. Unfortunately we were not able to complete that dataset. That information would allow precise identification of the previously mentioned "bottlenecks," analysis of the reasons for their occurrence and development of solutions. Another limitation is the lack of a "before and after" analysis using a similar observation period prior to the LH-related interventions, which could have provided more information on their influence on the workflow at our ED. In addition, a longer observation period (6 months or 1 year) would allow for a more thorough analysis. Furthermore, extending our study to other EDs would allow for generalization of the results and development of good practices regarding optimization of the work of these departments.

Conclusions

Although the LM methodology derives from the manufacturing sector, its tools are easily available and can be successfully implemented by healthcare staff in their daily work. Changes in the organization of work resulting from the use of LM (particularly the 5S and checklist techniques) at our ED/study site were positively assessed by the medical staff.

Conflict of interest

None.

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REVIEW ARTICLE

Distal transradial access via snuffbox for cardiac catheterization: a review

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Abstract

Vascular access is an essential component of coronary angiography and percutaneous coronary intervention. The choice of access site significantly impacts on procedural outcome. Distal transradial access (dTRA) via the anatomical snuffbox has emerged as an alternative to the conventional transradial approach. This article presents an analysis of dTRA, examining its anatomical considerations, procedural aspects, and clinical outcomes. While dTRA offers potential benefits such as improved patient comfort and a reduced risk of radial artery injury, challenges remain, including a steeper learning curve for operators and limitations in specific patient populations. This review aims to provide a comprehensive understanding of dTRA, enabling informed decisions regarding its adoption and advancement in contemporary cardiac catheterization.

Keywords: distal transradial access · snuffbox · cardiac catheterization · radial artery · vascular access

Citation

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Introduction

Transradial access (TRA) has become the preferred approach for cardiac catheterization, surpassing femoral access due to its reduced local complications and improved patient comfort [1-8]. However, a novel technique known as distal transradial access (dTRA) has emerged, offering potential advantages over the conventional TRA (cTRA) [9-10]. The dTRA involves cannulating the radial artery (RA) in the anatomical snuffbox (also known as the radial fossa or fovea radialis), a triangular depression located at the base of the thumb.

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This distal puncture site, compared to the traditional proximal RA access, provides distinct advantages [11-12].

The shift towards dTRA is motivated by its potential to reduce vascular complications, improve patient comfort and preserve the RA for future access [9-10, 13]. This preservation is critical, as the RA access may be required for subsequent procedures, including coronary or non-coronary interventions, arteriovenous fistula creation for hemodialysis or use as a graft in coronary surgery. These benefits stem from the anatomical characteristics of the RA in the snuffbox region [11]. This review aims to present the literature on dTRA through the snuffbox, focusing on its benefits, limitations and future applications beyond coronary procedures.

Material and methods

A literature search was conducted using PubMed and Google Scholar databases to identify relevant articles published in English about the use of dTRA. The search strategy incorporated a combination of keywords and their synonyms, including but not limited to: distal transradial access, dTRA, anatomical snuffbox access, distal radial artery access, cardiac catheterization, coronary angiography, percutaneous coronary intervention, PCI, transradial intervention.

Results

The search yielded 239 abstracts. After screening and a comprehensive assessment, 49 full-text articles (21 randomized controlled trials, 24 prospective and retrospective observational trials, 2 large registries and 2 meta-analyses) were deemed eligible for inclusion in this review.

Discussion

Historical aspects

The first mention of TRA in the literature dates back to 1948, when surgical cut-down provided access for aortic catheterization [14-15]. TRA for cardiac catheterization was pioneered by Campeau in 1989 and later developed by Kiemeneij and Larman in 1993 [16-17]. This was a paradigm shift in interventional cardiology because the TRA offers significant advantages over the traditional femoral approach, particularly in reducing access site complications [3-4, 8]. This has driven the widespread adoption of the TRA and led to continuous refinement of techniques and exploration of alternative access points along the RA.

The dTRA (also known as snuffbox access) emerged as a further advancement of the TRA. Kiemeneij is credited with pioneering this approach in 2017, recognizing the potential benefits of accessing the RA in the anatomical snuffbox [13]. Although the first mentions of accessing the dorsal RA for blood pressure monitoring in children and adults occurred nearly 50 years ago [18-19], and its usefulness for coronary and non-coronary procedures was reported by other researchers a few years before Kiemeneij, these early reports did not generate much attention or enthusiasm [20]. In 2011, Babunashvili and Dundua introduced a procedure utilizing dTRA access for retrograde recanalization of forearm RA within several days of an initial cTRA procedure complicated by occlusion [21].

Anatomy of the distal radial artery

This region, characterized by its superficial location and unique anatomical features, offered the possibility of minimizing vascular injury, enhancing patient comfort and preserving the proximal RA for future access. The key landmark for dTRA is the anatomical snuffbox, a triangular depression on the dorsolateral wrist which is best visualized when the thumb is extended. It is bordered by the tendons of the extensor pollicis longus (medially), extensor pollicis brevis and abductor pollicis longus (laterally) and the radial styloid process (proximally) [11, 22-23]. Its floor consists of the scaphoid and trapezium bones. The distal RA, the target for dTRA, passes through this region, located superficially beneath the skin (see Figure 1). This location facilitates easier access and potentially reduces the risk of deep punctures (see Figure 2).

The RA's distal anatomy contributes significantly to the safety of TRA. Near the anatomical snuffbox, the RA branches to form both the superficial palmar arch (anastomosing with the ulnar artery) and distally the deep palmar arch (anastomosing with the deep palmar branch of the ulnar artery). Interconnected by extensive collateral vessels, this robust dual-arch system ensures continued antegrade flow to the hand even if the distal RA is occluded, minimizing the risk of retrograde thrombosis [11, 22-25]. This anatomical characteristic is the key to its potential benefits in reducing radial artery occlusion (RAO):

- Preserved Blood Flow. Because the access site is located after the palmar arch branches off, therefore even if a thrombus were to form at the access site, blood flow to the hand can often continue through the palmar arch. This collateral circulation helps maintain perfusion and reduces the risk of hand ischemia.
- Lower Occlusion Risk. By preserving blood flow through the palmar arch, dTRA minimizes the duration of complete RAO during and after the procedure. This reduced occlusion time is considered significant factor in lowering the overall risk of RAO.

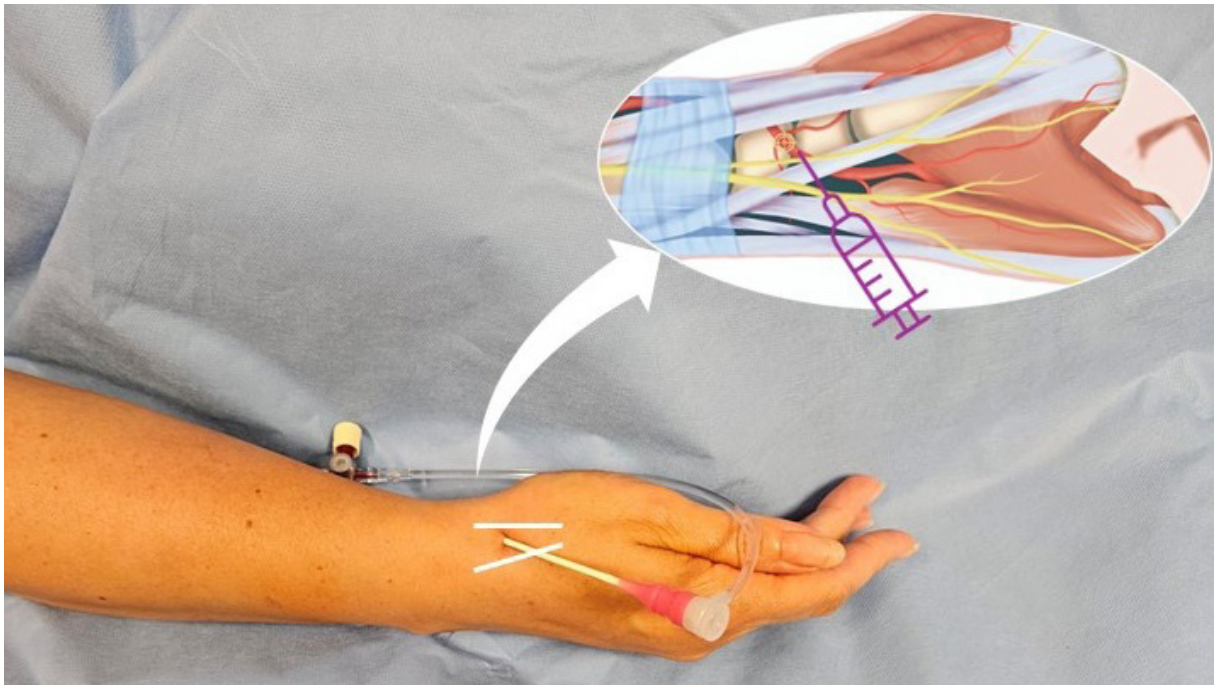

Figure 1. Distal transradial access via the anatomical snuffbox (fovea radialis)

White lines next to the arterial sheath indicate the boundaries of the snuffbox area: the tendon of the extensor pollicis longus (medially) and the tendons of the extensor pollicis brevis and abductor pollicis longus (laterally).

The snuffbox also houses the cephalic vein and branches of the radial nerve. The initial segment of the cephalic vein, is often prominent within the snuffbox. Branches of the radial nerve, responsible for sensation in the dorsal hand, are typically located deeper and lateral to the RA [11, 22-23]. While the superficial location of the RA in the snuffbox is advantageous, the smaller arterial caliber and proximity of tendons necessitate a thorough understanding of the anatomy for safe and successful cannulation without complications. It is important to distinguish dTRA within the snuffbox from the "very distal TRA," which involves puncture distal to the snuffbox and carries additional anatomical considerations [26]. This "very dTRA" modification was not assessed in this review because of insufficient published evidence regarding its efficacy and safety.

RA size

The success of dTRA is significantly influenced by the diameter of the distal RA [27-30]. Studies show that the distal RA is significantly smaller than the proximal RA, with average diameters ranging from 1.70 to 2.99 mm [30-43]. Reported distal RA diameter measurements vary due to inconsistent methods, including measurement techniques, anatomical landmark identification, vessel diameter definition (inner vs. outer) and study conditions. Studies conducted in European populations have report an average distal RA diameter of approximately 2.30 mm [30, 37, 43]. A strong positive correlation ($r = 0.66$) exists between the distal RA size and forearm RA size, with the distal RA measuring 80-89% of the forearm segment's dimension [30-32, 40]. Studies highlight a correlation between specific anthropometric and clinical factors and distal RA size. For instance, males have RA diameters that are on average 14% larger compared to females [30]. Furthermore, height, body weight, body mass index and body surface are consistently correlated with RA diameter [30, 32, 36, 40]. Certain comorbidities (e.g. diabetes and hypertension) are associated with smaller distal RA dimensions [40].

The reduced size of the distal RA, particularly in women and individuals with smaller body surface area, is correlated with technical difficulties for operators, potentially elevating the risk of complications (e.g. vasospasm or occlusion) [30]. Using larger vascular sheaths can exacerbate this challenge, as the size discrepancy between the sheath and the artery increases the likelihood of damage to the arterial wall and occlusion. Ultrasound-guided assessment of RA size, particularly comparing the distal and proximal segments and considering gender differences, is essential for appropriate patient selection, guiding procedural technique and minimizing complications [27]. In the absence of ultrasonography, a well-palpable distal RA pulse and a proximal RA pulse may indicate a satisfactory distal RA size, as there is a positive correlation between those two parameters ($r = 0.5$) [30].

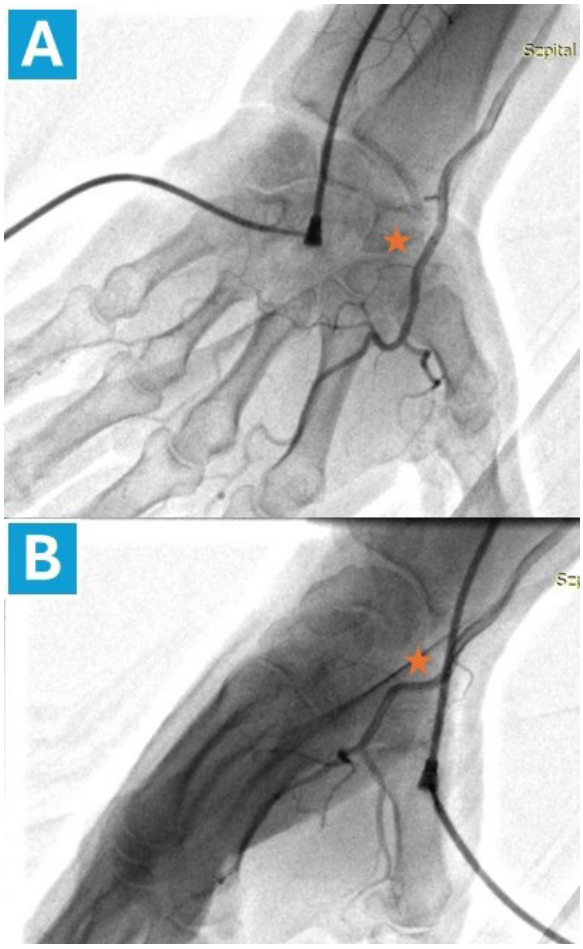

Figure 2. Angiography of the distal radial artery at the snuffbox

This angiogram was performed by administering contrast media through a sheath placed in the ulnar artery. The * symbol marks the site of distal radial artery puncture at the level of the snuffbox, visualized with the hand in pronation (A) and in a neutral position (B).

The dTRA technique

Numerous studies were focused on refining the technique for dTRA, with a particular emphasis on optimizing patient comfort during the procedure [12-13]. Ultrasound plays a crucial role in assessing the suitability of dTRA by measuring the distal RA diameter and identifying potential anatomical challenges [27]. This pre-procedural assessment allows for informed decision-making and selection of the most appropriate access site.

Patient positioning is another important element of successful dTRA. For right-sided access, the patient's arm should be placed neutrally alongside their body, with the lateral side facing upwards. Left-sided access can be achieved by either flexing the left hand medially towards the patient's groin or abducting the left arm on a supportive board for easier access. The patient's arm should be maintained in a neutral position throughout the procedure, which may be particularly beneficial for patients who are obese and those with limited range of motion in the arm. Both the left- and right-sided dTRA may improve the ergonomics of the procedure for both the patient (comfortable forearm position) and the operator (not leaning over the patient).

Once the patient is appropriately positioned, the operator should identify the optimal access site based on anatomical landmarks and the course of the distal RA [12-13]. A diminished RA pulse can be observed following the subcutaneous administration of an anesthetic (lidocaine or bipuvacaine), thus obscuring the ideal puncture site and necessitating additional access attempts. This may be attributable to anesthetic infiltration within the confined anatomical space of the snuffbox, potentially inducing vasospasm. Therefore, using smaller volumes of anesthetic (0.5-2.0 ml) are be recommended. The preferred technique for RA puncture is the modified Seldinger technique [12-13]. This approach involves directly accessing the arterial lumen with the needle and without traversing the posterior wall, as opposed to the through-and-through technique. Periosteal puncture at the base of the anatomical snuffbox can cause discomfort and potentially contribute to vasospasm and therefore should be avoided. Repeated punctures carry an inherent risk of iatrogenic arterial spasm, further complicating another puncture attempt. Therefore, maximizing first-attempt success is crucial. Due to the RA's curvature, the needle's angle relative to the skin will influence its entry angle into the vessel. To minimize the risk of arterial dissection, the needle should be slightly angled downwards (30°-45°) before advancing the guidewire. Due to their lubricity and flexibility, hydrophilic guidewires are recommended when navigating tortuous anatomy or encountering arterial spasm. If distal RA tortuosity impedes guidewire advancement, maneuvers such as pronating/supinating the hand or ulnar deviation can mitigate vessel curvature and facilitate passage. A combination of 2 or 3 spasmolytic drugs (typically nitroglycerin, verapamil or papaverine) effectively minimizes the risk of RA spasm.

Due to the anatomy of the distal RA, smaller arterial sheaths are generally preferred. Specifically, hydrophilic-coated slender sheaths are advantageous due to their smoother insertion. Thanks to their thin-walled design, the outer diameter is reduced by one French (Fr) size while preserving the inner diameter. Slender sheaths are commercially available in sizes 5 Fr, 6 Fr and 7 Fr.

Fluoroscopy or ultrasound guidance can be invaluable during guidewire insertion, particularly if there is any uncertainty about its positioning [27]. Visualizing the guidewire's path helps ensure proper placement within the artery and minimizes the risk of complications. Additionally, the pressure waveform from the introducer sheath can provide further

confirmation of successful access. Catheter selection for dTRA is determined by the same factors as for cTRA: patient anatomy and the particular procedure. In all patients undergoing dTRA, an additional 3-5 cm of catheter length should be factored in to accommodate the longer course of the artery, particularly in taller patients (> 185 cm in height). Therefore, diagnostic and guiding catheters exceeding the standard length of 100 cm are recommended. In clinical scenarios necessitating larger catheter sizes, a sheathless approach may be a viable alternative. Resistance during guidewire or catheter advancement at the level of the antecubital fossa may occasionally occur when using the left-sided access. This is attributable to arterial angulation secondary to joint flexion and transient forearm extension during passage typically mitigates this issue.

Learning curve of the dTRA

The adoption of dTRA has a significant learning curve [44-45]. Achieving and sustaining a high success rate (> 94%) required approximately 200 procedures [44]. As operator experience grew, both procedural duration and the number of access attempts decreased [44-45]. Furthermore, female sex (odds ratio (OR) 1.84, 95% confidence interval (CI) 1.01--3.39, p = 0.049) and systolic blood pressure below 120 mmHg (OR 1.87, 95% CI 1.04-3.36, p = 0.036) were identified as independent predictors of unsuccessful dTRA cannulation [44]. These findings underscore the critical role of operator experience and careful patient selection in optimizing dTRA success.

Radial artery occlusion

Table 1 presents collected data (including RAO rates) from two large registries and the available prospective randomized clinical trials (RCTs) on dTRA [46-70]. RAO is the main complication of TRA, precluding future access to the RA. Reported rates of RAO after cTRA vary significantly in the literature, ranging from < 1% to as high as 33% [71]. This variability partly stems from differences in the timing and methods used to assess RA patency. A meta-analysis of RCTs revealed an overall incidence of early (within 24 hours) RAO of 7.7% and 5.5% after 1 week follow-up, highlighting the need for standardized reporting and assessment of this complication [72]. Over the years, a decline in RAO rates down to 3.7% has been observed, reflecting a growing awareness and implementation of best practices aimed at preventing this complication [72].

The development of RAO is a complex process involving multiple contributing factors. Acute RAO occurs shortly after TRA, is primarily driven by arterial thrombosis due to a confluence of factors, including vessel wall injury induced by sheath and catheter manipulation, a localized hypercoagulable state and reduced blood flow due to hemostasis via compression [73]. In contrast, chronic RAO is characterized by a gradual thickening of the arterial wall, specifically the intimal and medial layers. This thickening results from the hyperplasia of vascular smooth muscle cells, representing a response to the initial injury [74]. Numerous randomized trials have established a clear understanding of the risk factors associated with RAO. These factors can be categorized as either modifiable or non-modifiable. Non-modifiable factors include female sex, low body mass index, diabetes and previous RA cannulation [72]. Modifiable risk factors for RAO include suboptimal sheath-to-artery ratio (> 1), inadequate anticoagulation, multiple unsuccessful puncture attempts, occlusive and/or prolonged hemostasis and RA spasm [72, 75].

The PROPHET study demonstrated that implementing the so-called patent hemostasis strategy (hemostasis with the preservation of blood flow) during cTRA significantly reduced the incidence of both early and late RAO. This approach resulted in a 59% reduction in early RAO and a 75% reduction in late RAO [75]. Furthermore, the PROPHET-II trial revealed that prophylactic ipsilateral ulnar compression during RA hemostasis, in conjunction with a patent hemostasis protocol, led to a significant decrease in RAO rates at 30 days post-procedure [76]. This combined approach resulted in an occlusion rate of 0.9%, compared to 3.0% without ulnar artery compression. Discrepancies in reported RAO incidence rates are partly due to inconsistencies in assessment methods and the limitations of pulse palpation. Even in the presence of significant occlusion collateral circulation can often maintain a palpable pulse, leading to an underestimation of true RAO rates [77]. Accurate determination of RAO incidence necessitates more objective evaluation methods, such as doppler ultrasound.

It was precisely the need for the reduction of RAO after TRA that was the main driver of the switch to the dTRA access. Initial observational studies on small groups estimate the rate of in-hospital forearm RAO after dTRA at 0% to 7% [13, 45-46, 78-82]. The majority of RCTs have demonstrated a lower incidence of RAO following dTRA compared to cTRA. This difference is often statistically significant, with reported RAO rates ranging from 0% to 5% for dTRA versus 0% to 13% for cTRA [46-60, 62-65, 69-70]. Importantly, none of the trials have shown inferior RAO outcomes for dTRA compared to cTRA. The ANGIE study, a larger trial in a Greek population, demonstrated a significant reduction in RAO incidence at 60 days post-procedure with dTRA (3.7%) compared to cTRA (7.9%; p = 0.014) [55]. The multicenter DISCO RADIAL trial included 1218 participants in Europe and demonstrated remarkably low RAO rates in both the dTRA (0.31%) and cTRA (0.91%) groups when measured until hospital discharge [60]. Although the difference in RAO rates wasn't statistically significant (p = 0.29), it is worth noting that both groups benefited from a strict hemostasis protocol adhering to current best practice recommendations, which likely con-

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access

Author name (Trial name)	Koutouzis [46]	Vefali [47]	Lin [48]	Sharma (*DORA*) [49]
Study type	RCT	RCT	RCT	RCT
Total sample	200	205	900	970
dTRA sample	100	102	450	485
cTRA sample	100	103	450	485
Diabetes (dTRA vs. cTRA)	27% vs. 28%	36.2% vs. 37.8%	10.7% vs. 12.4%	n/a
Procedure	CAG	CAG and PCI	CAG and PCI	CAG
Sheath size	6 Fr	5 Fr, 6 Fr	6 Fr	5 Fr, 6 Fr
Access time (dTRA vs. cTRA)	269 ± 251 s vs. 140 ± 161 s	46.85 ± 2.41 s vs. 36.66 ± 5.16 s	3.90 ± 2.50 min vs. 3.10 ± 2.40 min	n/a
RA spasm (dTRA vs. cTRA)	3% vs. 4%	0% vs. 4%	n/a	1% vs. 12%
Crossover rate	30% vs. 2%	5% vs. 4%	4% vs. 3.3%	4% vs. 2%
RAO at forearm (dTRA vs. cTRA)	5% vs. 9% (at discharge)	n/a	1.6% vs. 3.8%	2% vs. 13%
Follow-up	30 days	until hospital discharge	until hospital discharge	postoperative
Year published	2019	2019	2020	2020
Country	Greece	Turkey	China	India

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access (continued)

Author name (Trial name)	Eid-Lidt (*DAPRAO*) [50]	Wang [51]	Xiong [52]	Dadarwal [53]
Study type	RCT	RCT	RCT	RCT
Total sample	282	200	161	320
dTRA sample	140	100	81	160
cTRA sample	142	100	80	160
Diabetes (dTRA vs. cTRA)	51.4% vs. 43.7%	26% vs. 18%	9.9% vs. 5.0%	n/a
Procedure	CAG and PCI	PCI	CAG and PCI	CAG and PCI
Sheath size	6 F	6 Fr	n/a	5 Fr, 6 Fr
Access time (dTRA vs. cTRA)	2.7 ± 1.9 min vs. 2.7 ± 2.0 min	2.4 (1.7-4.2) min vs. 1.7 (1.4-2.3) min	86 ± 26 s vs. 74 ± 25 s	n/a
RA spasm (dTRA vs. cTRA)	3.5% vs. 4.2%	n/a	0% vs. 1.3%	n/a
Crossover rate	13.3% vs. 0.7%	2% vs. 6%	n/a	7.5% vs. 2.5%
RAO at forearm (dTRA vs. cTRA)	1 day: 0.7% vs. 8.4% 1 month: 0.7% vs. 5.6%	2% vs. 9% (at discharge)	n/a	0% vs. 5.2%
Follow-up	24 hours and 1 month	until hospital discharge	48 hours	until hospital discharge
Year published	2021	2022	2022	2022
Country	Mexico	China	China	India

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access (continued)

Author name (Trial name)	Lucreziotti [54]	Tsigas (*ANGIE*) [55]	Sanhoury [56]	Mokbel [57]
Study type	RCT	RCT	RCT	RCT
Total sample	204	1042	100	114
dTRA sample	104	518	50	57
cTRA sample	100	524	50	57
Diabetes (dTRA vs. cTRA)	30% vs. 28.8%	29.4% vs. 32.0%	50% vs. 54%	n/a
Procedure	PCI	CAG and PCI	PCI	CAG and PCI
Sheath size	6 Fr, 7 Fr	5 Fr, 6 Fr, 7 Fr	5 Fr	6 Fr
Access time (dTRA vs. cTRA)	137 ± 162 vs. 82 ± 95	120 (60-251) s vs. 75 (50-120) s	5.10 ± 1.61 s vs. 2.28 ± 1.16 s	n/a
RA spasm (dTRA vs. cTRA)	n/a	0.2 % vs. 0.0% (severe)	26% vs. 6%	n/a
Crossover rate	33% vs. 9.6%	21.8% vs. 5.5%	26% vs. 4%	n/a
RAO at forearm (dTRA vs. cTRA)	0% vs. 0%	3.7% vs. 7.9%	4% vs. 14%	0% vs. 6%
Follow-up	1 month	2 months	2 months	until hospital discharge
Year published	2022	2022	2022	2022
Country	Italy	Greece	Egypt	Romania

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access (continued)

Author name (Trial name)	Koledinskiy [58]	Daralammouri (*DARFORA*) [59]	Aminian (*DISCO Radial*) [60]	Oliveira (*DISTRACTION*) [61]
Study type	RCT	RCT	RCT	Registry
Total sample	264	209	1218	3683
dTRA sample	132	104	650	3683
cTRA sample	132	105	657	
Diabetes (dTRA vs. cTRA)	n/a	41.3% vs. 44.8%	30.2% vs. 28.9%	39.7%
Procedure	PCI	CAG and PCI	CAG and PCI	CAG and PCI
Sheath size	n/a	6 Fr	6 Fr GS	6 Fr
Access time (dTRA vs. cTRA)	125.1 ± 11.9 s vs. 58.8 ± 8.2 s	56.6 ± 61.1 s vs. 20.0 ± 18.4 s	median: 2 (1-4) min vs. 1 (1-3) min	n/a
RA spasm (dTRA vs. cTRA)	5.6% vs. 13.2%	3.8% vs. 2.9%	5.4% vs. 2.7%	n/a
Crossover rate	5.3% vs. 2.3%	1.9% vs. 1.9%	7.4% vs. 3.5%	2.5%
RAO at forearm (dTRA vs. cTRA)	0.8% vs. 6.2%	0% vs. 1.9%	0.31% vs. 0.91%	0% (palpation)
Follow-up	until hospital discharge	1 day and 14 days	until hospital discharge	until hospital discharge
Year published	2022	2022	2022	2022
Country	Russia	Palestine	Europe (multicenter)	Brazil

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access (continued)

Author name (Trial name)	Korotkikh (*TENDERA*) [62]	Al-Azizi (*DIPRA*) [63]	Acar (*The Litaunent*) [64]	Koziński (*ANTARES*) [65-67]
Study type	RCT	RCT	RCT	RCT
Total sample	776	251	700	400
dTRA sample	391	126	350	200
cTRA sample	385	125	350	200
Diabetes (dTRA vs. cTRA)	27.5% vs. 26.7%	34% vs. 30%	36% vs. 35.1%	32% vs. 34%
Procedure	CAG and PCI	CAG and PCI	CAG and PCI	CAG and PCI
Sheath size	5 Fr, 6 Fr	5 Fr, 6 Fr	5 Fr, 6 Fr, 7 Fr	5 Fr, 6 Fr
Access time (dTRA vs. cTRA)	42.0 (26.0; 84.0) s vs. 35.0 (23.0; 55.0) s	n/a	151.3 ± 73.9 vs. 73.4 ± 48.5	median: 140 (85-322) s vs. 80 (58-127) s
RA spasm (dTRA vs. cTRA)	23.5% vs. 22.8%	n/a	4.8% vs. 3%	19% vs. 4.5%
Crossover rate	5.1% vs. 0.8%	4.0% vs. 1.3%	15.6% vs. 5.7%	10% vs. 3.5%
RAO at forearm (dTRA vs. cTRA)	2.7% vs. 6.8%	0% vs. 1.6%	1.6% vs. 10%	1 day: 2.5% vs. 4.5% 60 days: 2.5% vs. 3%
Follow-up	90 days	1 month	2 months	1 day and 2 months
Year published	2023	2023	2023	2023
Country	Russia	USA	Turkey	Poland

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

Table 1. Chronological list of large registries and randomized clinical trials comparing distal vs. conventional transradial access (continued)

Author name (Trial name)	Lee (*KODRA*) [68]	Tehrani (*PRESERVE RADIAL*) [69]	Chen (*CONDITION*) [70]
Study type	Registry	RCT	RCT
Total sample	4977	64	801
dTRA sample	4977	33	398
cTRA sample	-	31	403
Diabetes (dTRA vs. cTRA)	36.8%	36.4% vs. 35.5%	18.8% vs. 20.3%
Procedure	CAG and PCI	CAG	CAG and PCI
Sheath size	4 Fr, 5 Fr, 6 Fr, 7 Fr	6 Fr GS, 7 Fr GS	6 Fr, 7 Fr
Access time (dTRA vs. cTRA)	median: 105 (65-180) s	55.5 ± 40.4 s vs. 42.4 ± 13.2s	median: 60 (50–90) s vs. 60 (50–60) s
RA spasm (dTRA vs. cTRA)	n/a	0% vs.6.5	n/a
Crossover rate	6.7%	3% vs. 0%	4.5% vs. 2.2%
RAO at forearm (dTRA vs. cTRA)	0.8% (palpation) 1.1% (ultrasound)	0% vs. 0%	0.8% vs. 3.3%
Follow-up	1 month	3 months	3 months
Year published	2023	2024	2024
Country	South Korea (multicenter)	USA	China

CAG – coronary angiography; cTRA – conventional transradial access; dTRA – distal transradial access; Fr – French (size); GS – glidesheath slender; n/a – not available; min – minute; PCI – percutaneous intervention; RCT – randomized controlled trial; s – second

tributed to the low overall RAO occurrence [60]. In the Brazilian DISTRACTION registry (3683 patients), there are no cases of RAO at discharge upon assessment by palpation [61]. A zero incidence rate, while impressive, might be influenced by the sensitivity of the detection method used. The South Korean KODRA registry is the largest (4977 patients) and reported a 0.8% RAO rate after 1 month detected upon palpation and a 1.1% rate when assessed by ultrasonography [68]. A recent meta-analysis of 15 randomized studies (7,196 patients, dTRA = 3,475, cTRA = 3,721), found a significantly lower risk of RAO in the dTRA group (1.8%) compared to the cTRA group (6.6%). This translates to a risk ratio of 0.31 (95% CI: 0.21-0.46, $p < 0.001$) favoring dTRA [9].

The anatomical advantages of dTRA likely contribute to its lower RAO rates. Even with distal RA occlusion during hemostasis, antegrade flow through the superficial palmar arch helps maintain perfusion and reduce retrograde thrombus propagation into the RA [13]. An experimental study simulating RAO in healthy subjects demonstrated a key difference between distal and proximal occlusion sites. While simulated occlusion at the wrist (proximal RA) led to significant flow reduction in the forearm RA, simulated occlusion in the anatomical snuffbox (distal RA) did not significantly impact flow [83]. Furthermore, the location of the superficial palmar branch within the anatomical snuffbox allows for efficient compression and faster hemostasis, further minimizing the risk of RAO development. Using thin-walled, hydrophilic sheaths during dTRA procedures can potentially lower the occurrence of RAO in both the forearm and the anatomical snuffbox [84].

The recently published prospective, multicenter 'Open Radial Artery Study,' might challenge the pursuit of novel dTRA techniques as its authors reported a reduction in RAO incidence after cTRA using a 'patent hemostasis' technique [85]. After 2 weeks, none of the 2181 patients who underwent the procedure experienced RAO. These impressive results were achieved by meticulously adhering to a protocol designed to minimize the risk of RAO using appropriate sheath sizes, anticoagulation, minimizing hemostasis time (60 ± 6 min) and verifying patency during hemostasis with plethysmography [85]. This highlights how that attention to such procedural details might be more crucial to reducing RAO occurrence than the choice of access site.

Non-RAO complications, access failure and access time

The use of dTRA has a high safety profile for non-RAO access-site complications, particularly bleeding. Real-world data collected after implementing best practices revealed a 3.3% incidence of dTRA-related bleeding. This breakdown included mild 1.1% BARC (Bleeding Academic Research Consortium) type 1 and 2.2% BARC type 2 bleeding [9, 68]. Importantly, there were no instances of severe or life-threatening bleeding events (BARC type 3 or 5) [68, 86]. Furthermore, mild hematoma (EASY grade I (Early Discharge After Transradial Stenting of Coronary Arteries Study)) occurred in only 3.1% of patients, while serious hematoma was exceptionally rare in a study population of approximately 5000 [68, 87]. Other potential complications (e.g. pseudoaneurysm or arteriovenous fistula) were infrequent and often detected via ultrasound. When recognized early, they can typically be managed with extended compression at the radial fossa. [88-89]. Transient, mild neuropathy, presenting as thumb numbness within a few hours post-procedure, are observed in up to 29% of individuals, likely due to radial nerve irritation [65]. Interestingly, data from two studies incorporated in the meta-analysis showed significantly greater post-procedural pain in dTRA compared with cTRA, with no differences in pain while accessing the RA [9].

Undeniably, the dTRA is more technically demanding than cTRA, as evidenced by higher rates of access failure and crossover, typically to the ipsilateral proximal RA. Early reports cited crossover rates as high as 30% [46]. A recent meta-analysis of 18 RCTs showed a significantly greater relative risk of crossover with dTRA compared to cTRA (10.3% vs. 3.7%, $p < 0.001$) [9]. The KODRA registry and a largest randomized trial (DISCO RADIAL), reported crossover rates of 6.7% and 7.4%, respectively [60, 68]. Factors potentially contributing to access failure include unsuccessful arterial puncture, limited operator experience, weak RA pulse, smaller RA diameter, lower body mass index, vasospasm and possibly female sex [60, 65, 68].

While meta-analyses did not demonstrate a difference in RA spasm rates between dTRA and cTRA, some authors report a higher incidence with dTRA (up to 19% vs. 4.5% for cTRA). This discrepancy may stem from differences in RA vasospasm definition and diagnostic methods (ideally it should be confirmed through angiography, see Figure 3). Regardless of the definition used, RA vasospasm can contribute to access failure. A recent study found that applying a transdermal nitroglycerin patch on the puncture site before dTRA significantly increased first-attempt success rates for those using palpation-guided techniques [90]. This improvement, attributed to a likely reduction in RA spasm, was accompanied by a noticeable increase in the average diameter of the distal RA [90].

Although dTRA requires a significantly longer mean access time when compared with cTRA (2.6 ± 1.8 vs. 1.8 ± 1.3 min; $p < 0.001$), the overall procedure time, contrast volume use and fluoroscopy time are comparable between the two techniques [9]. The dTRA does not influence the motor or sensory function of the hand, both in early and long-term follow-up [91-92].

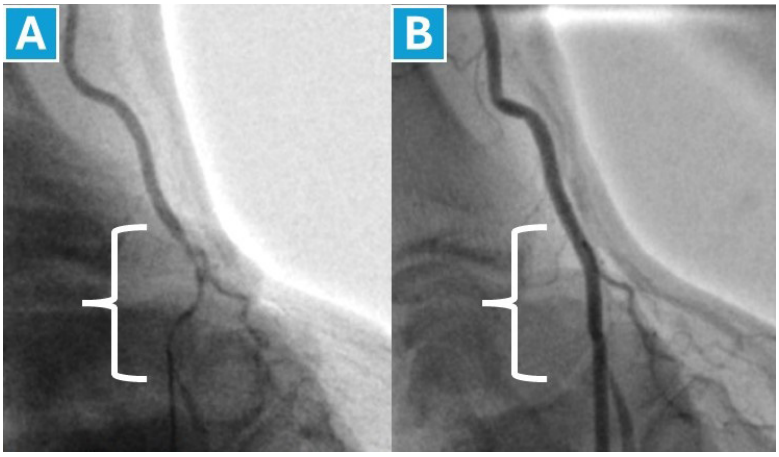

Figure 3. Severe distal radial artery spasm

This angiogram demonstrates severe spasm of the distal radial artery (A), during an attempt to advance a standard 0.018" J-shaped miniguidewire following puncture with a 22-gauge needle. Contrast media was administered through the needle to visualize the spasm. Image (B) shows the same radial artery after the spasm resolved.

Hemostasis

Following sheath removal, hemostasis is typically achieved more rapidly with dTRA compared to cTRA [9, 12]. Traditional radial hemostasis relies on distal wrist immobility, which may not be sufficient for the more mobile dorsal hand [12]. A more secure method involves tamponade with a gauze plug and elastic bandage at the access site. Alternatively, a dedicated dTRA hemostatic device can be employed. Its advantages are secure positioning and precise compression, achieving results comparable to the traditional gauze and bandage technique. Currently, only one such dedicated dTRA hemostatic device is commercially available (Preclude SYNC DISTAL radial compression device by Merit Medical Systems) [28]. Although many operators report successful use of hemostasis devices designed for cTRA.

Despite general agreement that dTRA requires shorter hemostasis times to balance RAO risk without increasing access-site bleeding, no standardized protocol has been accepted in clinical practice. Published data on optimal hemostasis time varies widely, ranging from 135 ± 62 minutes in a recent meta-analysis to 180 minutes proposed by some operators [9, 93]. In the largest studies, including the KODRA registry and DISCO RADIAL, the hemostasis time was 153 minutes [60, 68]. Preliminary unpublished data from our group suggests even shorter durations are feasible, with 90, 60 and 30 minutes routinely applied after 7 Fr, 6 Fr, and 5 Fr thin-wall sheaths, respectively. This inconsistency highlights the need for further research to establish a standardized, evidence-based protocol for dTRA hemostasis.

Coronary and noncoronary procedures via dTRA

Experienced operators can successfully use the dTRA for a range of coronary interventions, from straightforward procedures to complex scenarios e.g. high-risk interventions, chronic total occlusion and even ST-elevation myocardial infarction [81, 94-97]. With appropriate patient selection, comparable access times and overall procedural success can be achieved in myocardial infarction cases via dTRA as with cTRA [81, 95-96].

Beyond its established role in coronary interventions, dTRA has shown promise in carotid interventions, limb ischemia treatment, pelvic organ procedures, neuroradiology and even perioperative blood pressure monitoring [52, 96-99]. Preliminary reports indicate both the safety and high success rates of these procedures. It is very interesting to see reports of dTRA use in structural heart disease procedures. Achim et al. successfully utilized bilateral dTRA with an 8 Fr sheath in 32 high-risk patients with severe symptomatic aortic stenosis undergoing balloon aortic valvuloplasty [100]. They achieved a 100% technical success rate and most patients were mobilized within 24 hours.

Conclusion

Distal transradial access can be a versatile technique for percutaneous interventions. The data suggests that in the hands of experienced operators and after implementation of best practices, the dTRA offers efficacy comparable to cTRA, with potentially lower rates of RA occlusion, shorter hemostasis time and reduced bleeding complications.

Conflict of interest

The authors declare that they have no conflicts of interest.

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REVIEW ARTICLE

Melatonin as a potential treatment option in diabetes complications

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Abstract

Recent research indicates that disrupted sleeping and eating patterns along with ageing can contribute to the development of diabetes mellitus (DM) via effects on circadian rhythms and metabolic control. The use of anti-DM drugs alone is insufficient to achieve control of the reduction in β-cell function, insulin resistance, inflammatory mediation, oxidative stress and the DM-related complications. To prevent micro- and macrovascular DM complications, researchers are exploring the therapeutic potential of melatonin, a hormone secreted from the pineal gland with peak at night-time. We searched the Cochrane Library, PubMed and Google Scholar databases for relevant articles. Review articles, clinical research and case studies about the impact of melatonin on DM complications, the anti-oxidant action of melatonin, anti-inflammatory action of melatonin and the combination of melatonin plus DM drugs were included in this review. One hundred three articles that met our selection criteria, published between November 2004 and January 2024 were analyzed. This review aims to summarize the literature regarding melatonin's mechanisms of action and potential as a therapeutic option in the treatment of DM complications.

Keywords: melatonin · anti-oxidant · diabetes mellitus · complications

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Introduction

René Descartes described the pineal gland as "the seat of the soul." Today we know that the pineal gland's main role is to receive and convey information about the light-dark cycle through the secretion of melatonin, the so-called "darkness hormone" [1]. This endogenous hormone's secretion is regulated by circadian rhythms [2]. In addition, it plays an important role in glucose metabolism, along with its anti-aging, anti-cancer, and anti-inflammatory properties [3-4]. When the circadian rhythm is disrupted, incorrect signals of the central circadian timing system are sent and thus disrupting the release of melatonin and glucose homeostasis, that can even lead to DM mellitus [5-6].

DM mellitus (DM) is a chronic disease characterized by elevation in blood sugar concentration (hyperglycemia). There are two main types of DM: type-1 DM mellitus (T1DM, triggered by an auto-immune disease) and type-2 DM mellitus (T2DM, due to insulin resistance) [7-10]. Interestingly, melatonin has been associated with both types of DM. In T1DM, elevated plasma levels of melatonin and reduced insulin levels are observed, whereas T2DM is characterized by lower melatonin levels. This is consistent with the finding that melatonin and insulin antagonize each other [3]. This is because in T1DM the pancreatic beta (β) cells are destroyed leading to decreased insulin production and hyperglycemia, while the enzyme activation cascade stimulates melatonin production. However, in T2DM low melatonin levels cause higher mRNA expression of the melatonin receptors and insulin resistance enhances the elevation of insulin, resulting in β-cell exhaustion and elevated glucagon leading to hyperglycemia [11]. Unhealthy diet and obesity are commonly known risk factors for T2DM, while recent studies suggest that shift work and sleep disorders can also raise the risk of T2DM by disrupting circadian rhythms [12]. Patients with T2DM are frequently shown to have micro- and macrovascular complications [13-14].

Chronic and uncontrolled hyperglycemia leads to the formation of advanced glycated end products (AGEs), leading to the generation of reactive oxygen species (ROS) and stimulation of inflammatory cascade and resulting in DM complications [15-16]. Melatonin has anti-oxidant properties and emerging evidence suggests it reduces DM complications via amelioration of oxidative damage [17]. In addition to its role as a ROS scavenger, melatonin can alleviate DM complications via several mechanisms described in this review.

Both direct and indirect anti-oxidant properties of melatonin can protect our bodies and maintain health. Additionally, melatonin can have a potential role in the protection of mitochondrial action, modulation of the immune system, improvement in circadian rhythm control, modulation of the immune system and neuroprotective actions [18]. Unfortunately, as we age the levels of melatonin in our bodies decrease and this decrease is even more pronounced in people with insulin resistance-related diseases e.g. DM [19].

In this review we aimed to summarize the literature regarding melatonin's mechanisms of action and potential as a therapeutic option in the treatment of DM complications.

Material and methods

The literature search was performed, during the period between November 2023 and February 2024 on databases including the Cochrane Library, PubMed and Google Scholar. The keywords "melatonin", "anti-oxidant", "DM mellitus" and "complications" were used separately and in combination. Articles about the impact of melatonin on DM complications, the anti-oxidant action of melatonin, anti-inflammatory action of melatonin, and the combination of melatonin plus DM drugs were included in this review. We limited the search to articles published in English to ensure that the studies could be understood and assessed by the review team. Articles published in other languages and irrelevant to the research questions were excluded.

Results and discussion

The initial search returned 200 abstracts. After screening the abstracts, we conducted a thorough manual review of the 153 articles and found 103 that met our selection criteria, published between November 2004 and January 2024.

Mechanism of hyperglycemia toxicity

Chronic hyperglycemia can cause damage through several mechanisms e.g. increased glucose metabolism, decreased antioxidant enzyme capacity, protein kinase C (PKC) activation, irreversible protein glycation, AGE formation and an imbalance between ROS formation and elimination resulting in oxidative stress [20]. Glucose enters the cell and undergoes metabolism to generate electron donors used by mitochondria for energy production. However, when the glucose level exceeds the mitochondrial capacity, overload electron donors will form ROS e.g. superoxide [21].

Glutathione is a crucial antioxidant in cells but it needs to be reduced by glutathione reductase and this process requires a cofactor: nicotinamide adenine dinucleotide phosphate (NADPH). Hyperglycemia can lead to depletion of NADPH, thus limiting the generation of reduced glutathione and making cells susceptible to ROS activity. The increased hexosamine pathway flux is one of the associated mechanisms in DM, it contributes to complications and also generates ROS [22].

Hyperglycemia increases the formation of diacylglycerol (DAG), which activates the PCK pathway, promotes the expression of endothelial nitric oxide synthase and inhibits endothelin-1, thus supporting vasodilation. As tissues become insulin resistant, this pathway decreases the synthesis of nitric oxide and increases the synthesis of vasoconstrictor endothelin-1. Chronic hyperglycemia also directs the glycation of intracellular proteins, causing the formation of AGEs and affecting vascular function through increasing vascular wall stiffness [23].

Chronic hyperglycemia in the past can cause DM-related complications such as micro- and macrovascular diseases, even after normalizing blood glucose levels. This is due to the metabolic memory of tissues, including pancreatic β-cells. Thus, in order to control the progression of DM complications, it is important to control hyperglycemia [24].

Mechanism of anti-oxidative action of melatonin

Beyond the role of biological clock synchronizer, melatonin has pleiotropic activity, e.g. as an antioxidant [25]. Because of its lipophilicity, melatonin can cross the blood-brain barrier as well as the cell membrane to enter several tissues. It acts as a direct scavenger of reactive oxygen and nitrogen species, thus protecting the cell from free radical damage [26]. Additionally, melatonin has indirect anti-oxidant activity by stimulating the expression of several antioxidant enzymes and glutathione (a crucial low molecular weight non-enzymatic antioxidant) that work cooperatively with other antioxidants to enhance the mitochondrial electron transport chain [27]. In summary, melatonin and its metabolites inhibit the activity or expression of genes involved in free radical generation and upregulates the genes involved in free radical detoxification, as shown in Table 1.

Melatonin scavenges free radicals by enhancing antioxidant enzyme activity, therefore it protects the mitochondrial cell membrane, improves the electron transport chain activity, and enhances adenosine triphosphate (ATP) production [28]. A consequence of reactive species activity is lipid peroxidation, a naturally occurring metabolic process of alteration in the structure and function of the cell membrane, leading to a change in membrane fluidity which is the pathomechanism of ageing and several diseases. Melatonin is a stabilizer and inhibitor of the lipid peroxidation process via its ROS scavenger activity [29]. Moreover, melatonin can chelate metals such as iron, copper, cadmium, aluminum, zinc and lead, thus preventing their oxidative action and regenerating the activity of biological proteins such as collagen and insulin [30].

In addition to the anti-oxidant action, melatonin can inhibit the activation of nuclear factor-kappa B (NF-kappaB) a transcriptional factor which decreases the expression of inflammatory mediators such as cyclooxygenase (COX-2), tumor necrosis factor 1 alpha (TNF-1α) and inducible nitric oxide synthase (iNOS) [27]. Thus, melatonin is potentially helpful for a range of inflammatory conditions. Melatonin exerts anti-inflammatory activity by binding to macrophages and lymphocytes, blocking the transcriptional factors that trigger proinflammatory cytokines including hypoxia-inducible factor (HIF), nuclear factor Erythroid2-related factor 2 (NRF2), cyclic adenosine monophosphate (cAMP), cAMP response element binding protein (CREB), signal transducer and activator of transcription (STAT), peroxisome proliferator-activated receptors (PPARs) and activator protein-1 (AP-1) [31].

Table 1. Antioxidant effects of melatonin [32]

Reactive species that are neutralized by melatonin	Anti-oxidative enzymes that are stimulated by melatonin	Pro-oxidant enzymes that are inhibited by melatonin
Hydrogen peroxide	Glutathione peroxidase	Nitric oxide synthase
Hydroxyl radical	Superoxide dismutase	Lipoxygenase
Superoxide anion radical	Glutathione reductase	Myeloperoxidase
Alkoxyl radical	Catalase	Eosinophil peroxidase
Nitric oxide	Heme oxygenase	Cyclooxygenase-2 (COX-2)
Peroxynitrite	Glutamyl cysteine ligase	Inducible nitric oxide synthase (iNOS)
Singlet oxygen	Paraoxonase	
Hypochlorous acid		

Complications of diabetes

There are two major types of DM complications: micro- and macrovascular. The microvascular complications include retinopathy, nephropathy, and neuropathy. Whereas the macrovascular complications involve cerebrovascular disease, coronary artery diseases (CAD) and peripheral vascular disease [33-34] (Figure 1).

Chronic and poorly controlled hyperglycemia is the main factor that leads to DM complications which impair the quality of life and if not treated can even be life-threatening [35]. In addition to uncontrolled hyperglycemia, a sedentary lifestyle along with unhealthy diet, smoking, obesity, hypertension and hypercholesterolemia could increase the likelihood of developing micro- and macrovascular DM complications [36]. Inflammatory factors and external environmental factors that disrupt endocrine homeostasis may also play a major role in DM complications. As mentioned above, as individuals age, the secretion of the melatonin decreases, thus increasing the risk of DM complications [19].

Melatonin and microvascular complications

Diabetic retinopathy

Diabetic retinopathy (DR) is the major cause of blindness in patients with DM [37]. The pathophysiology of DR is linked to oxidative stress, inflammation, and autophagy [37]. The oxidative stress in the retina of a patient with DM is characterized by an elevation in ROS with a decrease in anti-oxidant enzymes e.g. superoxide dismutase. Additionally, hyperglycemia with retinal hypoxia resulting in overexpression of NADPH oxidase leads to overproduction of ROS. Moreover, the ROS activates the NF-kappaB transcriptional factor, which promotes the transcription of various genes, including those involved in the synthesis of nitric oxide and proinflammatory cytokines. Thus, using an anti-oxidant agent that increases the activity of superoxide dismutase can prevent the development of DR.

The other key factor of DR is chronic inflammation in which inflammatory cytokines including IL-1β, IL-8, IL-6, TNF-1α, and monocytes chemoattractant protein-1 cause microvascular cell loss and damage of the blood-retina barrier [38]. Melatonin indirectly inhibits NF-kappaB and subsequent inflammatory mediators, thus reducing retinal lipid peroxidation and nitric oxide activity, inhibiting COX-2 activity and neutralizing hydroxyl radicals [39].

In DR, autophagy has dual roles: sustaining the function of the retina and also it has deteriorating effects in the progression of retinopathy. In the early stage of DR, autophagy protects neurons and the blood-retinal barrier from damage, whereas in advanced stage the overexpression of autophagy causes cell death and retinal damage. Hyperglycemia also induces autophagy inside the retinal gliocytes known as Müller cells and can also cause lysosomal dysfunction, which hinders the autophagy. This dysfunction can lead to the accumulation

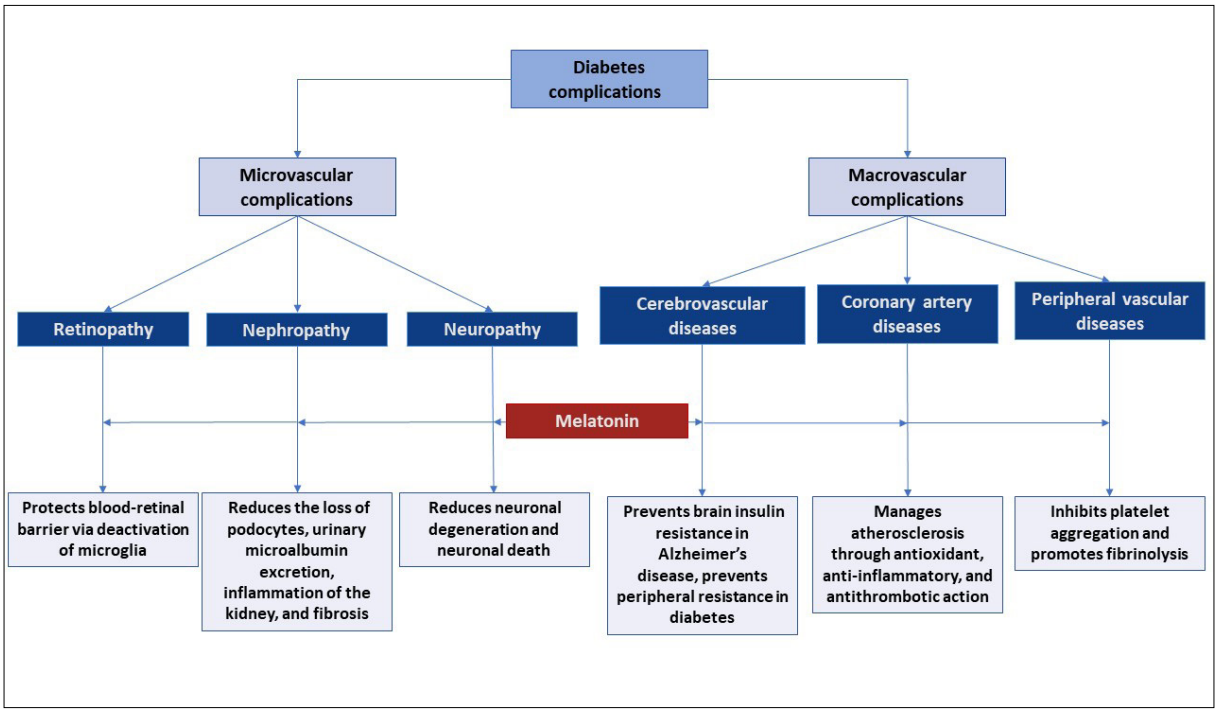

Figure 1. The potential roles of melatonin in DM complications

of cellular waste and stress within the Müller cells, which can result in the release of vascular endothelial growth factor (VEGF), a protein crucial for vascular function. Excess VEGF can cause abnormal blood vessel growth and leakage, leading to retinal damage and the development of DR [40].

In normal conditions, melatonin promotes autophagy for regulating cell survival, but during hyperglycemia and oxidative stress, melatonin indirectly inhibits autophagy through alleviating oxidative stress, inflammation, and endoplasmic reticulum stress and decreasing proinflammatory cytokines and VEGF [41-42].

Several clinical trials explored that the levels of melatonin secretion in proliferative DR patients are lower than in patients with non-proliferative DR and people without DM [43-45]. Wan et al. confirmed the lower level of plasma melatonin in DR and suggested that melatonin could be used as a biomarker for diagnosing this disease [46]. Moreover, administration of melatonin deactivates the microglia and prevents the death of epithelial cells in the retina via amelioration of oxidative stress, thus conserving the integrity of the inner blood-retinal barrier [47].

Diabetic nephropathy

Diabetic nephropathy (DN) involves kidney deterioration due to oxidative stress and is the major cause of end-stage renal disease in patients with DN worldwide [48]. It is characterized by glomerular hyperfiltration, nephron enlargement and mesangial cell hypertrophy, ultimately resulting in glomerulosclerosis [49]. Uncontrolled hyperglycemia with persistent ROS generation leads to apoptosis of several types of cells, including epithelial cells of the proximal tubule, damaging the nuclear DNA and mitochondria's genetic material that promotes loss of kidney function. Moreover, abnormal activation of the renin-angiotensin system (RAS) via various pathways such as PKC, adenosine monophosphate kinase (AMPK) and transforming growth factor-β (TGF-β) impact renal functions and lead to damage [50].

As an anti-oxidant, melatonin can reduce the oxidative stress markers of renal injury [51]. However, the nephroprotective activity of melatonin includes not only the anti-oxidant properties but is also demonstrated in reducing insulin resistance, decreasing blood glucose through improving insulin signaling, regulating glucose uptake by the renal tubules through its regulatory effect on glucose transporter (GLUT 1) and inhibiting the activation of RAS [52-54]. Therefore, by decreasing the loss of podocytes, reducing urinary microalbumin excretion, alleviating inflammation and fibrosis of the kidney, melatonin may increase renal recovery [42, 55]. Satari et al. investigated the positive effect of melatonin on improving metabolic parameters such as fasting blood glucose, total antioxidant capacity, glutathione levels, gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and high-density lipoprotein (HDL) levels in patients with DN after 12 weeks of administration [56]. Additionally, melatonin can inhibit renal ischemia-reperfusion injury among renal transplant patients by improving kidney function, ameliorating oxidative stress and inflammation [57].

Diabetic neuropathy

Diabetic neuropathy (DNP) is a nerve damage disorder resulting from hyperglycemia that induces oxidative stress, it includes autonomic, proximal, focal and peripheral neuropathy. Peripheral neuropathy is the most common and represents the main cause of altered gait, neuropathic pain, foot ulceration, and amputation [58]. Hyperglycemia, dyslipidemia and insulin resistance can lead to DNP, which enhance the activation of several pathways e.g. PKC, polyol, AGE formation, poly adenosine diphosphate-ribose polymerase (PARP) and loss of insulin signaling [59]. These metabolic alterations lead to changes in gene expression, abnormal ion current (increased sodium channel activity and decreased potassium channel activity), mitochondrial dysfunction, together with inflammation and oxidative stress resulting in nerve damage and cell death [60]. The neuroprotective action of melatonin occurs via several mechanisms including oxidative scavenger, immune-modulator, and anti-nociceptive effects [61].

The anti-apoptotic effect of melatonin in DNP results from the stimulation of PKC/NF-kappaB pathways that leads to the expression of PTEN-induced putative kinase 1 (PINK1), a protein that maintains mitochondrial health [62]. In addition to the role of melatonin in upregulating antiapoptotic proteins such as B-cell CLL/lymphoma (BCL-2), mammalian target of rapamycin mTOR, NF-kappaB, and WNT signaling pathways in high glucose-treated Schwann cells [63]. Melatonin could inhibit the endoplasmic reticulum stress and insulin resistance in T2DM through inhibition of apoptosis signal-regulated kinase 1 (ASK1), a protein that mediates apoptosis and cell death [64]. Additionally, one of the clinical trials assessed the efficacy of melatonin as an adjunct to pregabalin (150 mg) once daily to relieve the pain of DNP. Participants received a daily dose of 3 mg of melatonin for 1 week, followed by a daily dose of 6 mg for 7 weeks. The melatonin-treated individuals showed a significant decrease in DNP pain compared to the control group [65].

Melatonin and macrovascular complications

Atherosclerosis is the key pathological mechanism of cerebrovascular, coronary and peripheral arterial diseases, affecting arteries all over the body. It is a condition of plaque buildup inside arterial walls leading to the narrowing of

arterial lumen, decreasing blood flow, and potentially causing macrovascular complications. Hyperglycemia contributes to oxidative stress, inflammation, and endothelial dysfunction which collectively promote atherosclerosis in patients with DM [66].

Cerebrovascular disease

Cerebrovascular diseases including cognitive impairment, Alzheimer's disease and dementia are all correlated with DM complications, resulting from elevated intracellular glucose levels that lead to auto-oxidation of glucose, excessive ROS formation, disruption of vascular function and reduction in the brain blood flow, leading to neuronal injury and dysfunction [67]. Additionally, melatonin can neutralize the ROS and reduce insulin resistance in the T2DM patient with Alzheimer's disease [41, 68]. Furthermore, atherosclerosis in the cerebral arteries can obstruct and reduce blood flow to the brain causing stroke. A clinical study demonstrated the effectiveness of melatonin in improving functional and neurological recovery outcomes in patients with acute ischemic stroke when taken within 24 hours of the stroke symptom onset [69].

Coronary artery disease

Coronary artery disease (CAD) is considered the 3rd leading cause of mortality worldwide [70]. DM is a significant CAD risk factor in developed countries, with studies showing higher incidence of CAD among men and women with DM, than those without [71]. DM has a different impact on CAD mortality: women have a higher risk of mortality than men. Moderate hyperglycemia even without a DM diagnosis can increase the risk of CAD [72]. A meta-analysis by Berry et al. found significant differences in lifetime risks of cardiovascular disease among 257384 participants. ranked by, age, gender and race. They concluded that participants with high-risk factors (DM, hypertension, smoking, hypercholesterolemia) at any age were associated with substantially higher lifetime chances of CAD [73].

Atherosclerosis in the coronary arteries involves several pathological mechanisms, the major one is inflammation which triggers the formation of atherosclerotic plaque [74]. Deposition of the lipid, oxidative stress, endothelial dysfunction and differentiation of the vascular smooth muscles contribute to plaque formation [75]. The positive effects of melatonin on insulin resistance and lipid profile render it a good mediator for managing coronary artery disease in patients with DM [76]. Moreover, a link between melatonin secretion and reduction in systolic blood pressure has been shown. However no such association was found with diastolic blood pressure, indicating that the mechanisms that are not fully understood at this time [77].

Peripheral artery disease

Peripheral artery disease (PAD) is a complete or partial occlusion of the peripheral artery in the limb by an atherosclerosis plaque. PAD is the main cause of non-healing ulcers, limb amputation and mortality, particularly in patients with DM [78]. Animal studies have explored the effect of melatonin on heat-induced inflammatory and coagulation responses and they found that melatonin normalized platelet morphology and elevated fibrinogen levels following thermal injury [79-80]. In healthy young men, melatonin was associated with a significant reduction in fibrinogen levels, but no change in factor VII:C (a coagulation regulatory factor) and D-dimer levels [81]. Besides, melatonin could attenuate D-dimer elevations, suggesting limited thrombus formation and reducing atherothrombotic risk [82].

Platelet hyperactivity, increased prothrombotic coagulation factor activity, and impaired fibrinolysis are the main causes of an elevated thrombotic tendency in the context of low-grade chronic inflammation. The prothrombotic and inflammatory environment commonly observed in atherothrombotic disease may be favorably modulated by melatonin, thanks to its anti-inflammatory and antioxidative activity [83]. The anti-inflammatory, anti-hypertensive, anti--oxidative and anti-thrombotic properties of melatonin, make it a potential therapeutic option for reducing the risk of arterial occlusion in patients with DM. Otamas et al. showed the role of melatonin in preventing platelet aggregation and disruption of the clotting cascade by changing the structure of fibrin clots, in addition to promoting fibrinolysis [83].

Melatonin and the treatment of diabetes mellitus

The reduction of melatonin levels due to exposure to light at night and aging may lead to T2DM [84]. For that reason, the diurnal system could be regarded as a target for reducing the incidence of insulin resistance and DM [85]. The regulation of blood glucose by melatonin occurs through the direct binding to melatonin receptors (the receptors of melatonin are present in the pancreatic β-cells which modulates the secretion of insulin) [86]. Moreover, melatonin receptors are also present in other tissues, e.g. adipose, muscle and liver. Binding to these receptors causes different effects depending on the tissue type, e.g. in adipose tissue and muscle melatonin modulates the glucose transporters' expression, thus regulating glucose absorption by these tissues, while in the liver such binding will decrease hepatic gluconeogenesis [87-88].

Several human studies have revealed the efficacy of melatonin supplements in controlling fasting blood glucose when administered in low doses and for a short period

(about 3 months) [89-91]. According to the evidence, taking melatonin supplements can improve glycemic control, which can enhance the existing DM treatment [37]. A randomized clinical trial on patients with DM and CAD found that melatonin improved glycemic control, high-density lipoprotein-cholesterol, blood pressure, C-reactive protein, nitric oxide, malondialdehyde, glutathione and even mental health parameters (measured via Beck Depression Inventory) [90]. However, additional studies are needed to evaluate the effects of long-term administration of high dose melatonin on DM.

Although the effectiveness of melatonin in relieving DM with associated complications has been described in several studies, the use of melatonin remains an adjunctive therapy. In contrast to T1DM which is an auto-immune disease that is difficult to prevent, the progression of T2DM could be delayed by using certain medications [92]. Metformin is considered the first line treatment for T2DM due to its effectiveness and tolerability for patients [93]. However, metformin alone cannot control severe hyperglycemia and needs adjunctive therapies [94]. Subsequently, both metformin and melatonin have important potential to control DM and its complications, because melatonin can potentiate the effects of metformin [94]. Metformin combined with melatonin enhances renal function recovery in patients with DM who have chronic hyperglycemia. Additionally, the co-administration of melatonin-metformin improved glycemic control in T2DM patients [95-96].

The combination of melatonin and insulin can be used as effective therapeutants to prevent DN in diabetic rats. Melatonin and insulin possess nephroprotective properties by reinforcing the anti-oxidant enzymes and acting as free-radical scavengers. Renal diseases, such as fibrosis in DM, are triggered by inflammation, cell hypertrophy and kidney cell dedifferentiation. Inflammatory cytokines, e.g. TNF-α, IL-6 and monocyte chemoattractant protein-1 are linked to renal complications. In diabetic rats, elevated levels of these cytokines indicate altered innate immunity and chronic inflammation linked to insulin resistance. Combining melatonin and insulin can normalize pro-inflammatory cytokines and improve IL-10 levels in circulation. Melatonin reduces pro-inflammatory cytokines by reducing free-radical damage, while insulin increases anti-inflammatory cytokines, thus preventing DN [97].

The adjunctive action of melatonin and insulin can further decrease the hepatic damage along with improving glycemic control in diabetic rats [98]. The use of melatonin along with sulfonylureas (glibenclamide) shows significant regulation of ROS formation. Several animal studies on rats showed the role of exogenous melatonin together with glibenclamide in cell damage recovery from DM and cell function regulation, particularly in the epididymis [99-100]. The combination of melatonin with thiazolidinedione will show a potential anti-oxidant effect, due to the potent anti-oxidant properties of melatonin for scavenging the ROS and it is ability to decrease lipid peroxidation, in addition to the ability of thiazolidinediones in reducing oxidative stress by reducing hyperglycemia. Therefore, this combination might be effective in minimizing insulin resistance [101].

In recent years the use of melatonin and dipeptidyl peptidase inhibitors (DPP4-in) has significant therapeutic efficacy in DM, both have potent free-radical scavenging activity and anti-inflammatory properties. Such combination could overcome DM complications, particularly DNP and neuropathic pain [61]. The co-administration of sitagliptin and melatonin could be superior to monotherapy in the management of T2DM [102]. The combination of melatonin with sodium-glucose co-transporter inhibitors (SGLT2-in) can alleviate or prevent the ketoacidosis induced by SGLT2-in in patients with DM via inhibition of lipolysis and hepatic ketogenesis [6]. Additionally, in DM mouse models the combination of melatonin and DM therapy improved DM by regenerating β-cells and enhancing insulin sensitivity. Melatonin can promote propagation of β-cells, while sitagliptin promotes neogenesis of the β-cells, therefore they can promote β-cell redevelopment in the pancreas [103]. In Table 2 we summarized the therapeutic potential of combining melatonin with DM drugs.

Conclusions

Due to the global increase in DM mellitus incidence, it is crucial to discover new biologically active molecules that can effectively treat DM and its complications. Current treatments fall short of completely addressing insulin resistance, oxidative stress, impairment of β-cell function, inflammatory mediation and other pathological mechanisms linked to DM. Several preclinical and clinical studies demonstrated the role of melatonin as a potential DM treatment option to suppress microvascular and macrovascular DM complications. Thus, melatonin might be a promising therapeutant mainly due to its anti-oxidant and anti-inflammatory effects.

Moreover, in this review, we described the roles of exogenous melatonin (particularly when combined with DM medication) in enhancing and regulating the anti-oxidative process and preventing cell damage in the course of DM. Large-scale, randomized clinical studies are needed to elucidate the precise role of melatonin and its signaling pathways in the management of T2DM and its complications. Additionally, human clinical trials are required to assess the effectiveness of exogenous melatonin as monotherapy or combinational therapy for patients with DM.

Table 2. The potential role of melatonin as combined therapy with anti-DM medications

Type of combinational therapy	Actions	References
Melatonin + metformin	**In humans**	
	Melatonin potentiates the effect of metformin in managing DM	[94]
	Reduces HbA1C in patients with chronic DM	[95-96]
	Improves renal function recovery	
Melatonin + insulin	**In rodents**	
	May prevent DM-induced renal damage in diabetic rats	[97]
	May prevent hepatic damage in diabetic rats	[98]
	Improves glycemic control	
Melatonin + sulfonylureas	**In rodents**	
	Potentiates the anti-oxidant effect and regulate the production of reactive oxygen species	[99-100]
Melatonin + thiazolidinediones	**In rodents**	
	Potentiates anti-oxidant effect	[101]
	Decreases lipid peroxidation	
	Reduces insulin resistance	
Melatonin + DPP4 inhibitors	**In humans**	
	Overcomes DM neuropathy and neuropathic pain	[61]
	Enhances pancreatic beta cell regeneration	[103]
	In rodents	
	Potentiates anti-oxidant and anti-inflammatory activity	[102]
Melatonin + SGLT2 inhibitors	**In rodents**	
	Alleviates or prevents ketoacidosis in diabetic mice	[6]

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Conflict of interest

None.

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REVIEW ARTICLE

Ginger as a non-pharmacological prevention of postoperative nausea and vomiting (PONV): a review

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Abstract

Postoperative nausea and vomiting (PONV) are significant clinical problems associated with patients' unpleasant experiences and potential complications such as dehydration and electrolyte imbalances. In the search for effective methods of alleviating PONV, increasing attention is paid to the therapeutic properties of ginger. This review aims to summarize the current state of knowledge regarding the effect of ginger on reducing PONV. Analysis of conducted clinical studies suggests that ginger may be an effective agent in alleviating PONV after surgeries. Many of these studies indicate the beneficial effects of ginger, particularly when used in combination with conventional antiemetic drugs. Due to differences in methodology and inconclusive results in some studies, more research is needed to confirm these results and establish optimal doses and routes of administering ginger in clinical practice.

Keywords: ginger · PONV · postoperative nausea and vomiting · general anesthesia · antiemetic drugs

Citation

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Introduction

Postoperative nausea and vomiting (PONV) is a clinically significant complication that manifests within the first 24 hours post-surgery performed under general anesthesia and can last for more than 3 days. While considered an adverse effect of general anesthesia and a complication of surgical procedures, the exact causes of PONV are still not fully understood. It is known that the frequency of PONV is influenced not only by general anesthesia itself, but also by comprehensive perioperative patient care and various risk factors. PONV risk factors include female gender, history of motion sickness, history of PONV, non-smoking, prolonged anesthesia and the post-operative use of opioids [1]. PONV can occur in 20-30% of patients after surgeries [1-3]. The type of procedure also influences the frequency of PONV, e.g. after laparoscopic surgery it varies between 40% and 70% of patients [2, 4-5]. The use of volatile anesthetics during anesthesia and patient's age (< 50 years) can also increase PONV frequency. Apfel classified risk factors according to their association with the severity of PONV frequency (Table 1) and estimated the risk of PONV occurrence in patients with specific risk factors (Table 2) [6]. Although it can be helpful, the Apfel scale does not include many other PONV risk factors. Due to the complexity of the issue, anesthesiologists are unable to predict the occurence of PONV in any patient group. Nevertheless, the role of medical staff should not be underestimated because consideration of risk factors during selection of anesthetic drugs can reduce PONV episodes [6].

Table 1. PONV risk factors classified based on EbM and clinical significance (Apfel scale) [6]

Clinical significance	Risk factors	Risk
Certain and of particular clinical significance	female gender	+++
	non-smokers	++
	history of PONV or motion sickness	++
	general anesthesia compared to regional anesthesia	+++
	anesthesia with isoflurane, sevoflurane, desflurane, nitrous oxide	++
	prolonged anesthesia	++
	the use of opioids post-operation	++
Certain, but clinically less significant	young age and ASA 1 or 2 status neostigmine pyridostigmine	
Conflicting data	surgery anesthesiologist's experience gastric tube	
Insufficient data	pain change of body position	
Debunked	obesity (Body Mass Index) menstrual cycle, anxiety and personality	

Table 2. Simplified PONV risk scale [6]

Risk factor	Points
Female	1
Nonsmoker	1
History of PONV or motion sickness	1
Postoperative opioids	1
Total number of points	**Percentage frequency of PONV**
0	10%
1	20%
2	40%
3	60%
4	80%

The consequences of PONV include dehydration, electrolyte imbalance, cardiac arrhythmias, bleeding, hematomas, delayed wound healing, wound dehiscence, gastric content aspiration, esophageal rupture, subcutaneous emphysema or bilateral pneumothorax [1]. These complications reduce patients' quality of life, delay recovery and prolong the hospital stay [1-2]. Delayed hospital discharge also generates additional duties for medical staff and increases healthcare costs. Additionally, it was been estimated that PONV prolongs the stay in the post-anesthesia care unit by approximately 25 minutes [1].

Materials and methods

This review was based on literature available online in the PubMed database. Emphasis was placed on articles written in English and published from the year 2000 onward. The literature was selected to provide the broadest perspective on the topic and draw consistent conclusions. We used keywords "ginger", "PONV", "postoperative nausea and vomiting", "general anesthesia" and "antiemetic drugs".

Results and discussion

We found 66 studies and excluded 35 for the following reasons: lack of full text (n = 1), unrelated topic (n = 22), not in English language (n = 2), lack of placebo group (n = 4), summary of a study already included in our review (n = 2), published before 2000 (n = 4). Following the initial search, we selected 31 studies that met our criteria.

Are antiemetic drugs the best option we can offer?

The most common methods to reduce the risk of PONV include regional anesthesia, the use of propofol, and antiemetic drugs e.g. 5-HT3 receptor antagonists, antihistamines, antiparkinsonian drugs, anticholinergic drugs, promethazine and butyrophenones [2-3, 7]. To increase the effectiveness of therapy it is common clinical practice to combine antiemetic drugs that have different mechanisms of action [7]. Unfortunately, the above-mentioned drugs are associated with adverse effects e.g. excessive drowsiness, hypotension, dry mouth, dysphoria, hallucinations and extrapyramidal symptoms (e.g. dystonia, akathisia) [3]. Additionally, metoclopramide may cause headaches and diarrhea, while ondansetron may lead to transient elevation of liver transaminases [2]. Another disadvantage of synthetic antiemetic drugs is the necessity to use additional medications to alleviate adverse effects, leading to prolonged hospital stays and increased costs of care [4]. 5-HT3 antagonists (e.g. ondansetron) are most commonly used as prophylaxis on account of their higher efficacy in reducing the frequency of PONV compared to traditional antiemetic drugs like droperidol or metoclopramide. Due to numerous adverse effects the routine use of antiemetic drugs is not recommended, particularly in patients without PONV risk factors [7]. Additionally, the use of 5-HT3 antagonists is associated with higher treatment costs, prompting the search for relatively cheaper, widely available solutions with minimal adverse effects and drug interactions. Therefore, there is growing interest in herbal medicines and non-pharmacological methods [4].

Biological properties of ginger

Ginger (*Zingiber officinale*) has been used in Chinese and Iranian medicine for over 2000 years. Its unique properties allow for various applications, including the alleviation of gastrointestinal discomfort (primarily nausea and vomiting) as well as of symptoms caused by motion sickness, chemotherapy or gynecological interventions [3, 8-9]. One study has shown that compounds found in ginger root have antioxidant effects on free radicals that cause vomiting [4]. Additionally, ginger exhibits antagonistic effects on cholinergic (M3) and serotonergic (5-HT3 and 5-HT4) receptors, which is important in preventing PONV [10]. The main antiemetic substances found in ginger are gingerols and shogaols. Experimental studies revealed that 6-shogaol, 6-gingerol and zingerone inhibit the vomiting-inducing signal pathway in the afferent neurons of the vagus nerve through the suppression of 5-HT receptors, with 6-shogaol being the most potent inhibitor. The relative proportions of gingerols and shogaols are also important for ginger's effectiveness [11]. 8-gingerol is a 5-HT3 receptor antagonist in the ileum and 6-gingerol has been shown to enhance gastrointestinal transport [7]. Another mechanism includes the action of 6-, 8-, and 10-gingerols and 6-shogaol on the 5-HT3 receptor ion channel complex by binding to its modulatory site [9]. Galanolactone exhibits antiemetic effects through competitive antagonistic action on 5-HT3 receptors in the ileum [2, 7]. Besides its proven biological effects, it is important to emphasize that ginger is relatively inexpensive, widely available and its use is not associated with adverse effects [4, 7, 11].

Oral ginger

Montazeri et al. investigated the impact of ginger on PONV intensity. Authors divided patients randomly into an experimental group (received 4 capsules containing 250 mg of ginger 1 hour before surgery) and a control group (received 4 placebo capsules 1 hour before surgery). They reported that the frequency of nausea in the experimental group was lower at 2 and 6 hours post-operation compared to the placebo

group [12]. However, the difference at 2 hours post-operation was only slightly significant (p = 0.05). There were no distinct differences between both groups in the intensity of vomiting at any time point.

Albooghobeish et al. demonstrated the difference in the presence of PONV (p = 0.001) between two groups after laparoscopic cholecystectomy [4]. The intervention group received two 500 mg and one 250 mg capsules containing dried Ginger rhizome extract and the control group received 3 placebo capsules. The mean severity of nausea (measured using the Visual Analog Scale) in the intervention group changed from 7.92 ± 1.28 to 0.33 ± 0.67, while in the control group they changed from 8.00 ± 1.20 to 2.11 ± 1.55. Additionally, patients in the group receiving ginger capsules vomited less frequently and the use of antiemetic drugs was significantly lower than in the placebo group (p = 0.001).

Soltani et al. investigated nausea intensity and vomiting frequency at 0, 4, 8, 16 and 24 hours after laparoscopic cholecystectomy [10]. One group of patients received 500 mg of ginger orally 1 hour before surgery, while another group received 4 mg of ondansetron i.v. before the operation ended. Nausea intensity was significantly lower in the ginger group (except at 16 hours post-operation, Figure 1). However, the vomiting frequency did not differ between the groups.

Bameshki et al. demonstrated that oral ginger is effective in decreasing the severity of PONV after laparoscopic cholecystectomy [13]. One hour before surgery, the intervention group received 2 capsules containing 250 mg of ginger, while the control group received 2 placebo capsules. The severity of nausea distinctly changed in both groups (p = 0.001), however was lower in the ginger group (p = 0.078), with statistically relevant differences at 2 hours (p = 0.034) and 12 hours (p = 0.043). Although the incidence of vomiting was higher in the placebo group at 2 and 12 hours post-surgery, the number of vomiting episodes was statistically almost equal between both groups (p > 0.05).

Sedigh et al. investigated the effectiveness of ginger in preventing PONV after eye surgery [14]. The severity of nausea was lower in Group A (received 1 g of ginger 1 hour before the procedure) compared to Group B (received a placebo one hour before the procedure) immediately after recovery from anesthesia, as well as 15 minutes, 30 minutes and 2 hours after recovery (p < 0.05). Additionally, the incidence of vomiting also was significantly lower in the ginger group B (p < 0.05).

Beiranvand et al. administered ginger to reduce PONV among patients undergoing upper and lower limb surgery [15]. The intervention group received 4 ginger capsules 250 mg each, while the control group received 4 placebo capsules 2 hours before surgery. The intervention group had significantly lower incidence and severity of PONV at various time points after surgery compared to the placebo group (p < 0.05).

Sihombing et al. demonstrated that although adding ginger extract to beverages during the perioperative period significantly reduced the frequency of postoperative nausea (PON), it did not influence the frequency of postoperative vomiting [11]. Hewitt and Watts compared 6 trials measuring the effectiveness of varying doses of ginger powder in reducing PONV [5]. Evidence supporting the efficacy of 1-1.5 g doses is limited. Additionally, they suggested that there is no strong evidence supporting the use of either lower (< 1 g) or higher (> 1.5 g) doses of ginger powder. The authors noted that analysed studies had methodological flaws, thus their findings should be interpreted cautiously.

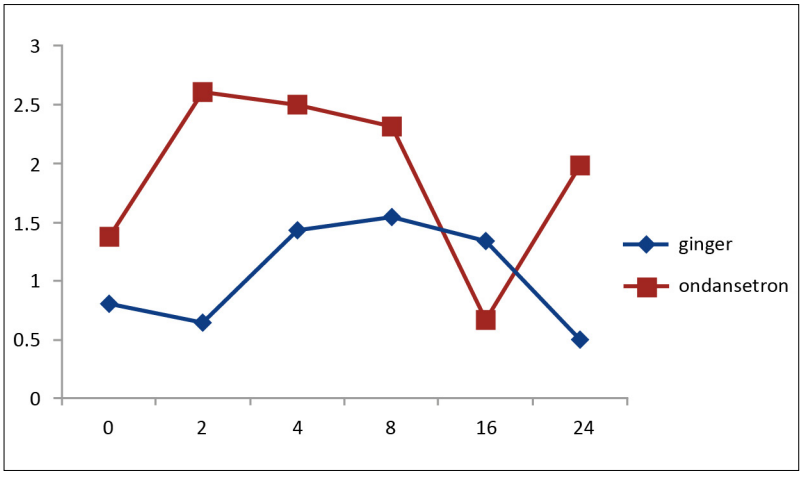

Figure 1. The differences in nausea severity between the groups studied by Soltani et al. [10]

Vertical axis – nausea severity measured using the Visual Analogue Scale (average scores); horizontal axis – hours after surgery

Aromatherapy with ginger oil

Hosseini and Adib-Hajbaghery [2] showed that the severity of nausea highly depends on the type of surgery and the presence of antiemetic intervention (p < 0.001). Authors compared open versus laparoscopic nephrectomy and also ginger essence versus placebo. Patients were divided into 4 groups (open surgery + ginger essence; laparoscopy + ginger essence; open surgery + placebo; laparoscopy + placebo), with two groups receiving ginger essence (two drops of ginger essence applied on gauze attached to the patients' collars) reapplied every 30 minutes for two subsequent hours. The mean nausea severity was reduced in both groups receiving ginger essence versus groups with placebo, but also

ginger essence showed higher effectiveness in patients after open nephrectomy than laparoscopic. The vomiting episodes were 2.92 ± 0.70 (open nephrectomy + placebo) versus 0.16 ± 0.37 (open nephrectomy + ginger essence). Additionally, the vomiting episodes were 6.0 ± 1.33 (laparoscopic nephrectomy + placebo) versus 1.39 ± 0.78 (laparoscopic nephrectomy + ginger essence) (Figure 2).

Adib-Hajbaghery and Hosseini [16] demonstrated that inhaling ginger essence has a positive effect on PONV after nephrectomy. The mean nausea intensity in the treatment group at the four subsequent time points was distinctly lower than in the control group ($p < 0.001$). Additionally, the differences regarding the number of vomiting episodes experienced by the treatment and control groups were statistically significant ($p < 0.001$). Sforza et al. [17] used ginger oil to treat nausea and vomiting after breast augmentation surgery. Participants received three drops of ginger oil (110 mg *Z. officinale*) or 3 drops of a placebo oil placed on their laryngeal mask before insertion in the larynx. The results showed that using ginger oil had a significant influence on PONV ($F(1, 18) = 73.05$, $p < 0.001$). The mean PONV score was 1.70 ± 0.48 and 4.20 ± 0.79 and the mean VAS score was 5.0 ± 1.63 and 5.9 ± 2.33 for the experimental group and control group, respectively. In their systematic review,

Arslan and Çelik compared the effectiveness of ginger aromatherapy versus placebo in PONV prevention. One study revealed that an oil mixture (containing ginger essential oil) and pure ginger oil reduced antiemetic consumption and the frequency of PONV [1]. Additionally, they reported that 7 out of 8 studies confirmed the antiemetic properties of orally administered ginger, while in 1 study no significant difference was found. In a study by Lee and Shin the experimental group received 0.3 ml of pure ginger essential oil inhalation after abdominal surgery, while the control group received a saline inhalation [18]. Nausea and vomiting scores were significantly lower in the experimental group. Additionally, the nausea and vomiting scores decreased distinctly in the first 6 hours after ginger essential oil inhalation.

Karaman et al. found a statistically significant difference in the nausea scores at 15 minutes ($p = 0.00$), with 2 drops of ginger and lavender essential oils outperforming rose oil and pure water [19]. Marsh et al. administered a custom blend of essential oils (including ginger) to the intervention group, which exhibited a statistically significant decrease in the need for antiemetics (by 22%; $p = 0.05$) [20]. Additionally, the total doses of antiemetics administered during the study period were significantly diminished (21%; $p \leq 0.05$).

Kiberd et al. reported that a blend of ginger, lavender, mint and spearmint aromatherapy had a non-significant effect on PONV in children compared with the control group [21]. However, the authors acknowledged that their pilot study had methodological flaws, which should be addressed.

Ginger combined with other drugs

Mandal et al. reported that the ginger-ondansetron combination (2 capsules with 0.5 mg ginger powder + 4 mg ondansetron i.v.) was significantly more effective than ondansetron alone (2 placebo capsules + 4 mg ondansetron i.v.) in preventing PONV [3]. Tavlan et al. concluded that a ginger-dexamethasone combination was not more effective than dexamethasone alone in preventing PONV among patients undergoing thyroidectomy [7].

Gynecological surgeries

Eberhart et al. found no notable differences between the 1st ginger group (300 mg of ginger powder), the 2nd ginger group (600 mg of ginger powder) and placebo group in terms of nausea, vomiting or the need for antiemetic medication following gynecological laparoscopy [22]. Apariman et al. administered 3 capsules of ginger to patients 1 hour prior to gynecological laparoscopy, while the control group B received 3 capsules of placebo. Ginger was effective in preventing nausea and it reduced vomiting within 6 hours post-operation (close to statistical significance) [23]. The effect of ginger powder on PONV was measured following major open gynecologic surgery and gynecological laparoscopy [24-25]. The authors observed statistically significant differences in nausea between both the ginger (1 g of ginger powder) and placebo groups. Nausea incidents

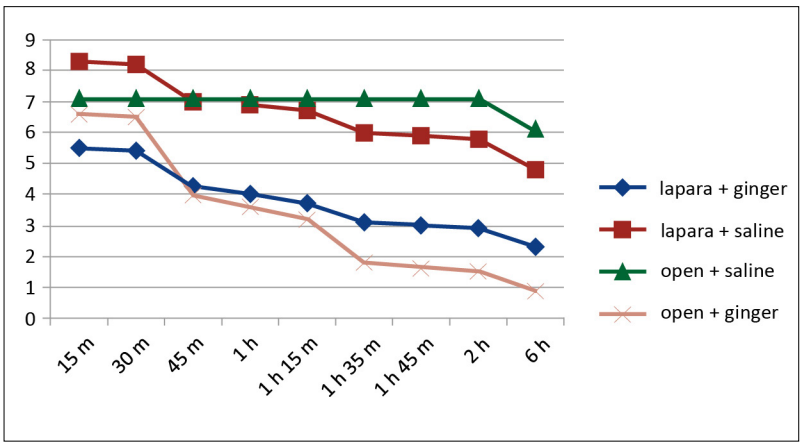

Figure 2. Changes in nausea mean scores in the groups studied by Hosseini et al. [2]

Vertical axis – nausea mean scores, horizontal axis – hours after surgery

and intensity were reduced in the ginger group. Additionally, the incidence and frequency of vomiting were lower in the ginger group, although the authors noted that these differences were not statistically significant [25].

Meta-analyses

In their systematic review and meta-analysis, Wang et al. reported that aromatherapy decreased the intensity of PON (standardized mean difference (SMD): -0.93, 95% CI: -1.64 to -0.22; p = 0.010) [26]. However, the reduction in episodes of vomiting was not statistically significant (SMD: -0.81, 95% CI: -1.98 to 0.37; p = 0.180). Although the subgroup analysis confirmed the effectiveness of ginger essence in PON management, due to considerable statistical heterogeneity and potential biases within studies, these findings should be interpreted cautiously. Arruda et al. explored the role of herbal medications, including ginger, in reducing PONV after laparoscopic or open obstetric/gynecological surgeries [27]. They reported a statistically distinct reduction in vomiting (relative risk [RR] 0.57; 95% confidence interval [CI] 0.38 to 0.86) and nausea (RR 0.69; 95% CI 0.50 to 0.96) with ginger compared to placebo. Additionally, the results suggested a statistically not significant reduction in the need for rescue pain medication in the ginger group compared to placebo.

According to Griffiths et al. it is doubtful whether ginger has any influence on the number of women experiencing intraoperative nausea during cesarean section under regional anesthesia [28]. Lu et al. reported that ginger reduces PON but does not cause any statistically significant difference in postoperative vomiting, combined rate of PONV and antiemetic drug use [28]. Therefore, the authors concluded that well-designed and rigorously conducted trials are needed to confirm the association between ginger intake and the risk of PONV.

Zhao et al. demonstrated that both ginger powder and ginger oil supplementation were effective in reducing the use of antiemetics and the intensity of nausea [29]. Ginger oil was superior to other forms of ginger treatment for the prophylaxis of postoperative vomiting (POV). Despite reducing the intensity of PON, ginger preparations did not show any obvious advantages in reducing the frequency of PON incidents.

Tóth et al. reported that ginger had a significant effect on reducing the severity of PONV (p = 0.019) and the results suggest that ginger reduces both the incidence of PONV and the demand for antiemetic medications [30]. Zhu et al. reported that ginger significantly outperformed placebo in terms of nausea severity, the percentage of rescue antiemetic use and the incidence of nausea and vomiting during the 6-hour postoperative period (for nausea severity: RR = 0.68, 95% CI = 0.55-0.85, p < 0.001; for rescue antiemetic use: RR = 0.78, 95% CI = 0.42-1.44, p = 0.43) [31]. The ginger group had a significantly decreased incidence of nausea in comparison to the preventive antiemetic group. Neither the frequency of vomiting nor the percentage of rescue antiemetic drug usage showed any appreciable variations.

Chaiyakunapruk et al. concluded that a fixed dose of > 1 g of ginger powder is more effective than placebo in preventing PONV [32].

Conclusions

Not all published studies confirm the effectiveness of ginger in reducing PONV. Further clinical research is needed to validate ginger's effectiveness, establish its optimal dose and route, and to develop precise recommendations for its use in clinical practice.

Conflict of interest

None.

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None.

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REVIEW ARTICLE

Game changer: understanding and managing hypertrophic cardiomyopathy in athletes

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Abstract

Physiological left ventricular hypertrophy in athletes often blurs the diagnostic line with hypertrophic cardiomyopathy (HCM), necessitating a critical differentiation to avert sudden cardiac death (SCD). This review explores various diagnostic approaches and proposes a well-founded strategy. The electrocardiogram (ECG) emerges as a highly sensitive HCM diagnostic tool, revealing characteristic changes in over 90% of cases. Holter monitoring aids in arrhythmia detection, yet its role in estimating SCD risk is subject to debate. Echocardiography encounters challenges in distinguishing HCM from normal athlete hearts. Cardiac magnetic resonance imaging (CMRI) enhances diagnostics by uncovering focal hypertrophy and fibrosis, with the absence of these markers not excluding HCM. Stress tests and family history provide invaluable diagnostic clues, and while genetic testing is not routine, its potential in uncovering hereditary factors is promising. Mandatory limitations on athletic activity for those with HCM are justified, given the heightened SCD risk during high-intensity sports. Extended diagnostic tests in borderline cases and universal screening for athletes are imperative for accurate risk assessment and the implementation of preventive measures. This comprehensive strategy integrates diverse diagnostic tools, ensuring a timely and precise identification of HCM, thereby mitigating the risk of SCD in the athletic community.

Keywords: hypertrophic cardiomiopathy · HCM · left ventricle hypertrophy · exercise induced cardiomegaly

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent form of primary cardiomyopathy, with an estimated incidence of 1 in 500 people, regardless of age [1]. The main characteristic of this disease is an increase of left ventricular wall thickness (LVWT), measured at end-diastole in any segment) reaching ≥ 15 mm. This hypertrophy cannot be convincingly explained by any other debilitating heart disease, (e.g, aortic stenosis, hypertension, ischemic heart disease) or endocrine disorders. With LVWT < 15 mm, HCM can be diagnosed if there are additional features of the disease, e.g. positive family history (particularly with unexplained LVWT > 13 mm in the first-degree relatives of the affected individual), myocardial fibrosis confirmed by cardiac magnetic resonance imaging (CMRI), asymmetric hypertrophy seen in echocardiography (echo) or abnormalities in the electrocardiogram (ECG) [2]. However, the presence of structural dysfunction (e.g. changes in papillary muscle structure) or the systolic anterior motion of the mitral valve (although its incidence reaches as high as 1/3 of HCM cases), is not mandatory to make the diagnosis of HCM [3-4]. Although HCM is inherited in an autosomal dominant manner and is linked to more than 1400 mutations in at least 11 major genes, pinpointing a specific mutation is not necessary for diagnosis [5].

Regular exercise, particularly endurance sports (e.g. cross-country skiing, rowing, long-distance cycling and running, swimming, soccer and tennis), can also cause myocardial hypertrophy and an increase in heart dimensions by about 10-20% as an expression of adaptation to a greater load [6-8]. It has been proven that the heart mass of athletes is greater than that of the population with a sedentary lifestyle [9]. Thus, a diagnostic problem of inestimable importance for athletes arises, because the diagnosis of HCM, which is not excluded by satisfactory physical performance [10], makes it necessary to significantly limit the physical activity undertaken even in the absence of symptoms and high-risk indicators, e.g. the presence of left ventricular outflow tract (LVOT) stenosis (either at rest or during physical exercise) or late gadolinium enhancement (LGE) in CMRI (indicating fibrosis) [11]. Our aim was to further dissect these diagnostic intricacies in order to contribute to the understanding and facilitating informed decision-making in the care of HCM in athletes.

Materials and methods

A comprehensive literature review was undertaken to gather insights into HCM among athletes and its distinction from the athlete's heart. Utilizing databases such as PubMed and Google Scholar, relevant studies focusing on HCM in athletes were identified using search terms like "hypertrophic cardiomyopathy," "diagnosis," "sudden cardiac death," "genetic mutations," and "athlete's heart" including their Polish equivalents. The search was limited to articles published in English and Polish. Articles were included if they examined specific aspects of hypertrophic cardiomyopathy (HCM) in athletes (e.g. its pathophysiology, clinical symptoms, diagnostic methods, treatments, genetic mutations and the latest developments). Studies that were not relevant to the above-mentioned topics (or were duplicated) were excluded.

Results

The initial search retrieved a pool of 100 abstracts. 65 articles comprising reviews, case reports, original research and clinical trials were meticulously selected based on their direct relevance to HCM in athletes, excluding duplicates or unrelated content.

Risk of sudden cardiac death

As mentioned in the Introduction, strict recommendations persist in the guidelines because when primary (and often undetected, asymptomatic) HCM is present, participating in high-intensity competitive sports can promote ventricular tachycardia/ventricular fibrillation. These arrhythmias consequently constitute a potent (yet modifiable) independent risk factor of sudden cardiac death (SCD), even if there are no traditional risk markers linked to the HCM [11]. This most likely occurs through the unpredictable exacerbation of electrophysiological abnormalities in HCM by stress, changes in blood volume, electrolyte concentrations and catecholamine output during sports [12-13]. Strongly in favor of restrictions for athletes with HCM is the fact that in 2007, established or suspected HCM accounted for 44% of SCD in young athletes [14]. In recent years, this percentage has decreased to 14.1% and

normal heart structure was more common in SCD cases [15]. This is likely due to the implementation of screening tests (e.g. ECG, physical examination, blood pressure measurement) in mandatory sports medicine examinations, which have significantly aided in identifying athletes at risk of SCD [16]. SCD in young athletes is quite rare (estimated at 1:50,000 people), but it is noted that there are many predicted years of healthy life for those affected and the mortality rate is 2.8-fold higher, compared to the non-athlete, same age population. A considerable portion of these untimely deaths stem from hereditary, asymptomatic heart abnormalities that manifest during physical exertion [17-18]. Hence, the need for screening seems all the more justified in this group, and The European Society of Cardiology (ESC) advises formal examination for all young professional athletes (usually 12-14 years of age) including history-taking and physical examination, family history gathering, and 12-lead ECG [19-20]. However, it should be emphasized that over 90% of exercise-induced SCD cases occur in amateur athletes, in whom screening options are nonetheless limited [21]. Furthermore, the incidence of SCD in a 10-year observational study of 10.9 million marathoners and half-marathoners were much lower, reaching 1:259,000, with HCM remaining the most important cause, confirmed in post-mortem studies [22-23]. Furthermore, after identifying patients via initial tests, a highly efficient risk stratification algorithm (proposed by AHA and ESC) can be applied to implement primary prevention of SCD [2, 14]. This involves the implantation of a cardioverter-defibrillator (ICD), which has significantly lowered the HCM-related mortality to 0.5% per year in the general population [12]. Prophylactic ICD implantation is not advised for athletes who do not meet the general indications to allow them to participate in competitive sports due to possible device-related complications (e.g. lead displacement (3.1%), infection at the implantation site (1.5%), swelling, bleeding or bruising, haematoma (1.2%), pneumothorax (1.1%) [11].

Electrocardiography

Electrophysiological manifestations of training, on the ECG, are generally divided into those caused by increased parasympathetic activity and those resulting from altered dimensions of the heart cavities. Some healthy athletes may have bradycardia or sinus arrhythmia at rest (usually correlated with respiratory rhythm), nodal rhythm, 1st degree atrioventricular (AV) block or 2nd degree Mobitz 1 AV block, which resolves with mild exercise. As for ventricular conduction, the criteria for left and/or right ventricular hypertrophy, incomplete right bundle branch block and sometimes J-point elevation with ascending ST segments may be met [25-26]. The elevated ST segment typically has a concave shape in the posterior and lateral leads, while convex elevation in the precordial leads is infrequent [27]. In the context of athletes, even if there's cardiac axis deviation and the criteria for atrial and/or ventricular enlargement are met on the ECG [28], we consider these as variants within the normal range [29]. Unless accompanied by symptoms (physical or subjective) and family history, there's usually no need for further diagnostic investigation. As with structural changes of the heart, male endurance athletes present the most ECG changes. In athletes younger than 14 years of age, there are differences in the changes presented, with more frequent T-wave inversion in the V1--V4 leads, although after 16 years of age these changes revolve spontaneously [30]. Therefore, in all Caucasian athletes ≥ 16 years of age, T-wave inversions in leads other than III, aVL, aVR, or V1 should raise diagnostic concerns [27, 31].

At the same time, ECG stands out as the most sensitive test for HCM, showing abnormalities in over 90% of cases [32]. Characteristic and most common abnormalities in HCM not seen in healthy athletes are deep T-wave inversions in lateral and/or posterior leads (occurring in 93% regardless of the amount of physical activity), horizontal or downsloping ST segment depression (in 47%). Other less common include pathological Q-waves (Q/R ratio > 0.25), in 27% and left bundle branch block. On the other hand, deep inverted T-waves (so-called "giant negative T waves") in the precordial leads may be indicative of the mid-ventricular or apex variant of HCM [26, 29, 33-34]. The aforementioned changes, even despite the absence of abnormalities in echo, should prompt greater diagnostic vigilance and broader investigations (see Table 1).

Table 1. The most common electrocardiogram (ECG) changes in HCM

Deep T-wave inversions ("giant negative T waves") in lateral/posterior leads (93% of cases)
ST-segment depression (47% of cases)
Pathological Q waves: Q/R ratio > 0.25 in lateral/posterior leads (27% of cases)
Deep T-waves in precordial leads: suggest mid-ventricular or apex variant of HCM

Dynamic Holter ECG

Holter ECG is not strictly a diagnostic tool for HCM, but it is often essential for capturing co-occurring arrhythmias. Recent studies have demonstrated the superiority of 14-day monitoring over the routinely used 24-48-hour monitoring in detecting non-sustained ventricular tachyarrhythmias (NSVTs, defined as lasting < 30 seconds) which are the most prevalent cause of SCD in HCM. Multiple bursts of NSVT are associated with increased risk (particularly in young patients) and should encourage further diagnostics. Another possible arrhythmia is ventricular tachycardia (VT), which if intolerable for the patient could be an indication for either implanting an ICD or treatment with β-blockers or amiodarone for secondary prevention. In other cases, starting treatment is not advised, as there is no evidence to suggest that sustained (> 30 seconds), monomorphic and well-tolerated VT predisposes to SCD more than non-sustained ventricular tachycardia (NSVT) [2, 35].

Echocardiography

Frequently observed echocardiographic changes in athletes include a 10-20% increase in LVWT and a 10-15% increase in both ventricular cavities dimensions compared to the similar age and weight population. Numerous studies were undertaken to ascertain the upper limits of physiological left ventricular hypertrophy (LVH) in athletes, leading to a consensus set at 10 mm for Caucasian women and 12 mm for Caucasian men, whereas in athletes of black African or Afro-Caribbean ethnicity, ventricular hypertrophy is greater and these limits were adjusted to 11 mm for women and 14 mm for men. The greatest changes in the Caucasian population are observed in male endurance athletes with a large body surface area, e.g. cross-country skiers, rowers, long-distance cyclists and runners, swimmers, soccer and tennis players [36-37]. These data were confirmed by CMRI studies [31]. However, only 2% of them achieve LVWT exceeding 12 mm [38] and among adolescent athletes, only 0.4% exceed 11 mm [39]. In extreme cases these values can raise diagnostic doubts whether to diagnose HCM or not, resulting in the so-called "gray zone", comprising < 2% of athletes who present LVH higher than the acceptable norm for this population but below the value of 15 mm that meets the criteria for HCM [24]. In such cases, expanding the diagnosis with additional tests (e.g. ECG, CMRI, exercise testing) is sufficient to confirm or exclude the diagnosis of HCM [10]. The first step should be a reevaluation of the LVWT to exclude measurement error (for example, due to erroneous expansion of the dimension by trabeculae carneae, papillary muscles or the moderator band). This should be followed by the comparison of these findings with an ECG examination. This is because every athlete eventually diagnosed with mild HCM had an abnormal ECG in the past. Structural and functional parameters alone were not enough to distinguish them from a healthy population exhibiting hypertrophy due to physical activity. Also, the uniform pattern of LVH in the athlete's heart differs from the asymmetric septal hypertrophy observed in 60% of HCM and apical hypertrophy in 10% of HCM. In contrast, LV cavity dilatation in athletes compensates for hypertrophy resulting in normal end-diastolic volume, which is typically reduced in HCM and compensated by hyperdynamic radial LV systolic function [3, 40].

Doppler evaluation of LV wall and diastolic mitral inflow patterns together with new methods allowing the precise evaluation of tissue distortion (e.g. measuring two-dimensional strain-derived velocity, strain, strain rate) can detect little disfunctions in long-axis relaxation which often occur a few years before the onset of obvious LVH in HCM. On the other hand, athletes often show above normal diastolic function, demonstrating high rates of early mitral inflow and early tissue relaxation by Doppler and high stroke volume even at elevated heart rates which, in combination with increased oxidative capacity and capillary conductance in skeletal muscle, translates into high VO_2 max during exercise [8, 40]. A study comparing echocardiographic parameters of athletes and non-athletes with HCM reported higher diastolic filling values in the former group, most of which were within normal limits (93% of athletes had an E/E' of < 12, 60% a septal E' ≥ 0.09 m/s and 87% a lateral E' ≥ 0.09 m). Hence, normal diastolic parameters and high VO_2 max do not rule out the diagnosis of HCM in athletes [33].

In addition to reduced diastolic function and low VO_2 max, features that may suggest a diagnosis of HCM include exercise-induced arrhythmias, reduced longitudinal systolic function and regional abnormalities of LV wall motion. The reduced longitudinal systolic function is assessed via global longitudinal strain (GLS) and is connected with an increased risk of heart failure (HF) even in the presence of a normal LV ejection fraction [41-42]. Although GLS at rest in athletes with HCM can be comparable to a control group of healthy athletes (who tend to have it slightly lowered), in general the average two-dimensional GLS in the group with HCM is reduced and its reduction in basal LV segments is a potential early indicator of HCM [43-45]. However, recent studies propose that changes in global and regional strain may not be useful in evaluating athletes, as they are a variant of the norm in this population [46].

In summary, an image eminently indicative of HCM in an athlete with LV hypertrophy (13-16 mm) would be a relatively small LV cavity (about 50 mm), hyperdynamic LV systolic function, dynamic LVOT stenosis during exercise, and in addition evidence of asymmetry of hypertrophy in regional/global strain (see Table 2) [8]. However, this clinical picture is quite rare given the variety of athletes' hearts and we are usually

dealing with equivocal findings that can be classified only after additional studies.

Cardiac magnetic resonance imaging

In the case of ECG changes and the absence of characteristic features or the presence of borderline abnormalities on echo, CMRI can more accurately reveal focal hypertrophy, especially of the posterior septum, apical and the free wall of the heart. Delayed enhancement after LGE, particularly in the region of the largest hypertrophies, can reveal typical features of cardiac fibrosis and influence the prognosis of HCM [31]. However, the lack of LGE does not rule out the diagnosis because it is not seen in as many as 60% of patients with HCM [47]. Additional changes may include elongation of the anterior mitral valve leaflet, the presence of an apical-basal LV myocardial bundle, abnormal position of the papillary muscles or myocardial crypts (see Table 3) [45]. These changes are suggestive of a diagnosis of HCM in suspected patients, particularly in family members carrying a pathogenic mutation without obvious changes in echo [48].

Stress testing

In the section on echo, it was shown how the dilatation of the heart cavities compensates for LVH in athletes and therefore high VO_2 max is observed. Virtually all athletes with HCM are thus asymptomatic and their excellent exercise capacity does not rule out a diagnosis of HCM. Although a VO_2 max > 50 ml/kg/min usually indicates an athlete's heart [33, 49]. Nevertheless, increased physical activity may reveal characteristic arrhythmias, decreased GLS in an athlete with HCM, abnormal blood pressure response (flat curve or even a drop due to abnormal vascular tone combined with small vessel ischemia and exercise-induced LVOT stenosis [50]), delayed return of the heart to resting rhythm, increased LVOT gradient and less pronounced increase in stroke volume. The role of echo and CMRI stress testing is ancillary to concerns unresolved by other tests [51]. CMRI perfusion studies can also reveal areas of subendocardial exercise-induced ischemia, which never occurs in the athlete's heart and is strongly suggestive of HCM (see Table 4) [52].

Table 2. The differences in the echocardiography in HCM and athlete's heart

Echocardiography	HCM	Athlete's heart
LV wall thickness (LVWT)	Increased	Increased by 10-20%. LVWT >11mm is found in 0.4% of adolescent athletes and >12mm in only 2% of adult athletes
Hypertrophy pattern	Asymmetric septal hypertrophy (60% of cases), apical hypertrophy (10% of cases)	Uniform LVH
LV cavity	Reduced	Normal end-diastolic volume
LV outflow tract (LVOT)	Reduced	Normal
Diastolic function	Reduced, low VO_2 max	Normal
Global longitudinal strain	Reduced, particularly in the basal segments	Normal

Table 3. Cardiac magnetic resonance imaging (CMRI) changes in HCM

Focal hypertrophy: in the posterior septum, apex and free wall
Late gadolinium enhancement (LGE): cardiac fibrosis
Elongation of the anterior mitral valve leaflet
Abnormal papillary muscle positioning
Myocardial crypts

Table 4. Exercise-induced cardiac changes in HCM

Blood pressure	Abnormal response
ECG	Characteristic arrhythmias
ECG Holter	NSVTs and VT
Delayed return of the heart to resting rhythm	Reduced
Echocardiography	Less pronounced increase in stroke volume
CMR	Subendocardial exercise-induced ischemia

Genetic testing

During initial testing, careful consideration should be given to a family history of sudden unexplained death, particularly in individuals < 50 years of age or documented cases of HCM within the family. If 1st degree relatives present with suspicious ECG changes this can also be a diagnostic clue [31]. Identification of a variant with some pathogenicity in a person with suspicious features on other tests can confirm the recognition of HCM and expedite similar diagnosis in other family members, but genetic testing should not be performed routinely [10], because in 40%-50% of patients with HCM the genetic basis is unknown and the various genetic mechanisms responsible for the pathophysiology of this disease remain largely enigmatic [53-54]. The diverse functions of these genes, e.g. encoding proteins that regulate calcium flow, building the cardiac sarcomere and Z-disc, influence the heterogeneity of the clinical picture of this disease. Moreover, it seems that the cardiac risk in gene-positive-phenotype-negative patients is similar to the population risk and current guidelines do not exclude such individuals from competitive sports after confirming the absence of abnormalities in echo and CMRI studies [5, 11]. In asymptomatic carriers of known pathogenic variants, LVH most often appears between 12 and 20 years of age and is not accompanied by any symptoms. Some of them will never present with full-blown HCM, and in some the disease may not appear until middle age [5, 55-56].

Discussion

Detraining

Since most athletes diagnosed with HCM are asymptomatic, no treatment is offered and they undergo follow-up, which provides a definitive opportunity to verify the diagnosis. Indeed, it has been proven that LVH associated strictly with prolonged, intense exercise regresses and after a 6-week period of training cessation the heart returns to a normal size range [57]. While there are also insights that reverse cardiac remodeling also occurs to some degree in athletes with HCM and is hard to distinguish from remodeling in healthy athletes; which in turn may be incomplete and persist despite long periods without activity [58-60]. It seems that further studies on larger groups will allow better decision-making about the complete suspension of training, which obviously has a significant impact on the life of an athlete.

Can sport cause cardiomyopathy?

There is one more issue that further complicates the picture of HCM in athletes. Namely, recently emerging studies that may support the development of secondary HCM due to the influence of intense exercise. A three-fold higher incidence of LGE has been demonstrated among experienced marathon runners, compared to the sedentary lifestyle population (12 vs. 4%), along with elevated markers of myocardial damage in this group, which is most likely related to a transient impairment of LV relaxation during increased cardiac action [61-63]. The significance of these parameters is not fully known, but a single small-group CMRI study conducted immediately after the marathon showed no obvious signs of myocarditis [64]. A study involving rats subjected to treadmill exercise for 16 weeks described LVH, diastolic dysfunction, and diffuse atrial and right ventricular fibrosis. In electrophysiological studies exercising rats also presented ventricular tachyarrhythmias more frequently than sedentary rats (42% vs. 6%) [65].

These results were not confirmed by a study on 114 Olympic athletes in endurance sports who intensively trained to 2-5 consecutive Olympic Games. No deterioration of cardiac function or arrhythmias was noted [66]. Moreover,

it has been proven that people engaging in the most grueling sports have longer life expectancy than those with sedentary lifestyle, which may be related to the observed prevention of age-related decline in elasticity and compliance in physically active individuals, which predisposes to cardiovascular disease later in life [67-68].

It is also important to briefly mention the performance-enhancing substances (doping) that can disrupt the picture of myocardial damage in athletes. The most cardiotoxic of these substances are androgen anabolics, which cause LVH and LV dysfunction (including arrhythmias), which along with a worsening of lipid profile and elevated blood pressure can lead to myocardial infarction [69]. LVH and myocardial fibrosis can also be caused by human chorionic gonadotropin and human growth hormone [70].

Conclusions

Diagnosing HCM in athletes is complex due to the overlapping physiological changes from exercise. Risk assessment for SCD relies on comprehensive, multifaceted screening methods like family history, ECG, echo, CMRI, and stress testing. While strict guidelines advise limiting activity in diagnosed cases, it is crucial to individualize management, considering evolving research on exercise-induced cardiomyopathies. Furthermore, implementing universal athlete screening and considering genetic testing in suspicious cases could enhance early detection and preventive measures, thus mitigating the risk of SCD in this population. Genetic testing offers insights but its routine use is not recommended. Detraining may reverse some cases, showing the adaptability of heart muscle. Emerging studies suggest exercise-induced secondary cardiomyopathies, needing further investigation and evaluation in relation to the undeniable health benefits achieved through physical activity.

Conflict of interest

The authors declare that they have no conflicts of interest.

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REVIEW ARTICLE

Is the treatment of glaucoma limited to topical drops only?

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Abstract

Glaucoma is a degenerative condition characterized by progressive loss of retinal ganglion cells, leading to irreversible vision loss. This review aims to summarize the current knowledge about treatment strategies that optimize and improve glaucoma patients' outcomes. We explored various therapeutic options for glaucoma, highlighting the importance of methods beyond the traditional topical eye drops. We discussed the pharmacological options, as well as the more individualized treatment approaches e.g. surgical interventions and laser therapy. Moreover, we described the role of neuroprotection (e.g. antioxidants, anti-inflammatory agents, NMDAR inhibitors). Further research is needed to confirm the efficacy and safety of these neuroprotective agents. Regarding neovascular glaucoma, we focused on anti-VEGF agents and panretinal photocoagulation. Finally, we analyzed the potential adjunctive role of statins in the treatment of glaucoma. Although there is conflicting evidence regarding the efficacy of statins as a potential adjunctive glaucoma treatment, recent studies suggest possible benefits of this therapy.

Keywords: glaucoma · implants · neovascular · MIGS

Citation

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Abbreviations list

- AH – aqueous humor
- anti-VEGF – anti-vascular endothelial growth factor
- CAIs – carbonic anhydrase inhibitors
- CO2 – carbon dioxide
- DNA – deoxyribonucleic acid
- GDDs – glaucoma drainage devices
- HMG-CoA – β-hydroxy-β-methylglutaryl coenzyme A
- IOP – intraocular pressure
- LPI – laser peripheral iridotomy
- MIGS – minimally invasive glaucoma surgery
- MP-TSCPC – micropulsetransscleralcyclophotocoagulation
- NMDAR– N-methyl-D-aspartic acid receptors
- NPGS – non-penetrating glaucoma surgery
- NOS – nitric oxide synthase
- NVG – neovascular glaucoma
- OAG – open-angle glaucoma
- POAG – primary open-angle glaucoma
- PGAs – prostaglandins agents
- ROS – reactive oxygen species
- SLT – Selective laser trabeculoplasty
- THC – tetrahydrocannabinol
- Δ^8-THC – Δ-8-tetrahydrocannabinol
- Δ^9-THC – Δ-9-tetrahydrocannabinol
- TPLI – thermal laser peripheral iridoplasty

Introduction

Topical eye drops, as well as surgery and laser treatment, are the only proven methods of lowering the intraocular pressure, which is the best-known modifiable risk factor for the development of glaucoma [1-2]. The essence of this neuropathy is degeneration and progressive loss of retinal ganglion cells, resulting in the optic nerve changes [1]. Therefore, various therapeutic options that seem promising in preventing or slowing down the degenerative process and saving the function of the optic nerve should be considered. Hence, our review focuses on methods such as neuroprotection including reduction of oxidative stress, neuroinflammation and excitotoxicity (increased level of intracellular calcium, resulting in the damage of the plasma membrane, cytoskeleton, DNA and other cellular components), as well as the controversial use of statins or vascular medications in neovascular glaucoma. Our goal was to select articles that describe glaucoma treatment and summarize them in terms that non-ophthalmologists can understand, to expand their knowledge and help them provide the best care for their patients.

Material and methods

We searched the Medline database for articles published from 2010 to February 2024 in English and Polish. The chosen articles show both basic, advanced, and new methods of glaucoma treatment. The inclusion criteria were: full-text article, on-topic (glaucoma treatment). Case reports and letters to the Editor were excluded from the review.

Results

Drops, oral drugs and bimatoprost implant

Despite the development of numerous therapeutic options, it is impossible to discuss glaucoma treatment without mentioning the first-line therapy: topical eye drops. Six groups of drugs are available in the form of eye drops: prostaglandin agents, beta-blockers, carbonic anhydrase inhibitors, α2-mimetics, rho-kinase inhibitors and cholinomimetics [3]. If monotherapy with eye drops is insufficient to lower the intraocular pressure (IOP), switching to medication from another group should be considered before prescribing an additional topical drug [4-5] (see Figure 1). There is no equal target IOP for all patients, so it should be determined individually. The factors that facilitate setting the target IOP are glaucoma stage, age, life expectancy, value of IOP before the treatment, and glaucoma progression rate [6]. If the pace of vision loss is dynamic, the target IOP should be decreased. The elderly or patients with long life expectancies should have treatment aimed at lower IOP.

Carbonic anhydrase inhibitors (acetazolamide and the less commonly used methazolamide) are also available in pill form. They reduce the production of aqueous humor (AH) by inhibiting the transport of bicarbonates to the posterior chamber, which leads to decreased IOP levels [6]. Acetazolamide is prescribed to prevent the acute progression of glaucoma, for example in primary angle closure glaucoma or secondary glaucoma induced by the use of other medication (e.g. adrenergic agents, steroids, tramadol) [6-7]. The recommended dose of 250-1000 mg per day should be lowered in patients with renal impairment. Acetazolamide increases the elimination of bicarbonates in the urine, which can lead to metabolic acidosis. Patients with chronic lung diseases are more likely to develop metabolic acidosis, so before prescribing the drug, it is necessary to evaluate lung function (by examining arterial blood gas or pulmonary function tests) [6].

Hyperosmotic medications may also be useful in glaucoma therapy because their influence on intracellular fluid flow Decreases IOP. Intravenous mannitol is used as the last-line

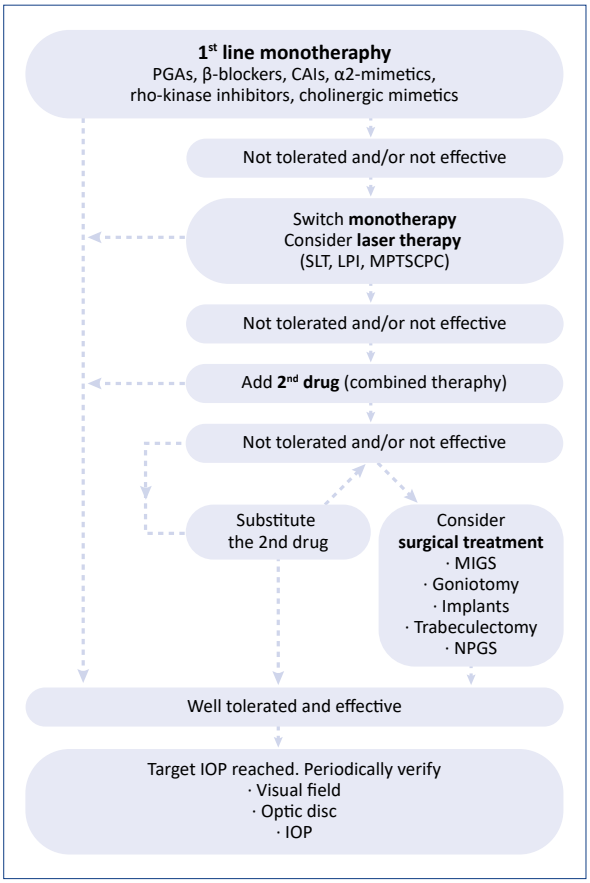

Figure 1. Suggested steps in the treatment of glaucoma

therapy [8]. Glycerol and isosorbide can be prescribed as oral drugs as well. Adverse effects of hyperosmotic medications include dehydration, increased diuresis and concentration of glucose, so they should be administered carefully to patients with diabetes mellitus [9]. Other adverse effects include nausea, vomiting, mental confusion and acute kidney insufficiency [5].

As implied by its name, the bimatoprost implant contains a prostaglandin analog. The implant is injected in the anterior chamber of the eye, where it constantly delivers bimatoprost to the ciliary body for about 3-4 months and acts more effectively than topical drops [10-12]. It is presumed that bimatoprost has a dual mechanism of action: reduces IOP by acting on the prostaglandin receptors in the trabecular meshwork which promotes the conventional outflow of AH and increases the outflow of AH through uveoscleral routes. Bimatoprost implants can be used in the treatment of open-angle glaucoma or ocular hypertension [10]. Due to decreased IOP, the complications of glaucoma (damage to the optic nerve and visual loss) are reduced [10]. The most common adverse reactions include irritation, pain, itching, watering of the eye and headache [13].

Laser therapy

The application of laser beam to the trabecular meshwork to improve AH outflow was introduced in 1972 [14]. Since then, improvements in laser technologies have led to their greater safety and effectiveness [15]. Currently, laser procedures target two main pathways of glaucoma treatment: decreasing AH production and increasing the aqueous outflow [16]. The European Glaucoma Society Guidelines recommend the following laser procedures: laser peripheral iridotomy (LPI), laser trabeculoplasty, thermal laser peripheral iridoplasty (TPLI) and cyclophotocoagulation [5].

Selective laser trabeculoplasty is the first choice in primary open-angle glaucoma. It is suggested that the therapeutic mechanism of SLT influences protein expression in the trabecular meshwork leading to increased AH outflow [17]. The most common indications of SLT include lack of compliance with treatment, anti-glaucomatous drops intolerance or pregnancy. Also, SLT is the appropriate approach in secondary open-angle glaucoma (e.g. pseudophakic glaucoma, pseudoexfoliation, pigmentary glaucoma) [15]. The Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) has demonstrated the safety and effectiveness of SLT in glaucoma treatment, it can reduce the medication burden and potentially improve patients' quality of life [17-18].

LPI is recommended in primary angle closure glaucoma. The laser beam is used to create a full-thickness hole in the peripheral iris, in order to connect the anterior and posterior chambers and avoid the pupillary block [15]. LPI is the standard of care for acute primary angle closure glaucoma, which can potentially lead to blindness [19]. Also, LPI can be performed in the treatment of secondary angle closure glaucoma, where it lowers the IOP and prevents optic neuropathy. In addition, LPI can be done as a glaucoma prevention strategy, however such a decision needs precise clinical evaluation including the presence of risk factors (e.g. family history) [15].

Acute primary angle closure requires emergency intervention to immediately lower IOP and resolve the pupillary block. The strategies include medical treatment and laser peripheral iridotomy and primary lens extraction [20].

Laser peripheral iridoplasty applies low-energy laser burns to the peripheral iris to widen the anterior chamber angle. The expected outcome is immediate shrinkage of collagen and gradual contraction of a fibroblastic membrane, pulling the angle open mechanically. The procedure is applicable either as a stand-alone treatment for non-pupillary block angle closure or as an adjunctive therapy for pupillary block angle closure. Moreover, it has high effectiveness in treating reversible angle closure [15]. In cases when laser iridotomy is not effective in overcoming the pupillary block, surgical peripheral iridectomy is necessary.

Cyclodestructive techniques have been an available for the treatment of refractory glaucoma since the 1930s and their current version is micropulse transscleral cyclophotocoagulation (MP-TSCPC) [21]. Cyclophotocoagulation involves the destruction of the ciliary body structures (via damaging ciliary epithelium and blood vessels or coagulative necrosis) to decrease aqueous production and regain control of intraocular pressure. There are two approaches – external (transscleral) and internal (endoscopic) cyclophotocoagulation [15].

Surgical treatment

Although they are not first-line treatment, surgical procedures might be the only chance to preserve vision in patients with refractory glaucoma. When it comes to the progression of nerve cells' damage due to the glaucomatous process, patients might even be unaware of the advancement of the disease and because of that, they are often referred to surgical treatment too late. Several surgical techniques (e.g. trabeculectomy and its modifications) have been widely in use for years and some are getting more popular now due to less invasive procedures which are referred to as minimally invasive glaucoma surgery (MIGS) [5, 22].

MIGS may be considered in patients with primary open-angle glaucoma (POAG), pigmentary glaucoma and pseudoexfoliation glaucoma but also in cases of adverse drug reactions or non-compliance with treatment. Contraindications include primary and secondary angle-closure glaucoma, active neovascular glaucoma, corneal opacity, or angle dysgenesis [23]. MIGS procedures can be divided into the *ab interno* approach with a clear corneal incision that spares the conjunctiva and the *ab externo* approach, which refers to scleral or conjunctival incision [24-26]. *Ab interno* MIGS is considered safer due to the protection of the conjunctiva (allows uncomplicated operations if needed in the future) [27]. Devices used in MIGS can be assigned to the anatomical areas where their action is intended. Schlemm's canal targeted implants work by: bypassing the trabecular meshwork (which is presumed to be blocked in open-angle glaucoma), dilating the canal, removing a portion of the trabecular meshwork or by penetrating deep into the Schlemm's canal and trabecular meshwork, which creates a sclerotomy [22]. Suprachoroidal stent facilitates AH drainage by creating a patent lumen from the anterior chamber into the suprachoroidal space, which promotes AH outflow via the newly-formed pathway [27]. Subconjunctival shunts bypass the trabecular meshwork, create a new drainage pathway, or divert AH from the anterior chamber to the subconjunctival space [22]. MIGS procedures minimize tissue trauma, offer fewer complications than traditional surgical approaches and reduce the duration of postoperative care, therefore they are an attractive alternative to conventional surgery [28-30].

For decades, trabeculectomy was the most widely used surgical procedure in glaucoma treatment due to its well-established long-term efficacy [5, 31-32]. This form of treatment is recommended for patients in whom other forms of therapy have either failed or are not likely to achieve target IOP using medications or laser therapy at the very beginning. The procedure involves creating a flap in the sclera and is followed by partial removal of the trabecular meshwork and Schlemm's canal. If a piece of the iris is removed as well, the procedure is called iridectomy. Although a lot of changes in newer techniques (e.g. MIGS procedures, newer implants or shunts) have been introduced, among clinicians and patients there is a relatively high concern about complications [27, 33-34]. They can be so serious that reoperation may be needed [32]. For example filtering blebs scarring or leakage, aqueous misdirection (which is characterized by a shallow central and peripheral anterior chamber, displacement of the lens and normal or elevated IOP), bleb overfiltration with hypotony maculopathy, choroidal detachment, partial vision loss or even blindness [32-37].

A procedure with a similar name (trabeculotomy) that can be performed alone or as combined therapy with trabeculectomy [5]. It can be used in the surgical management of childhood glaucoma. Trabeculotomy lowers IOP via disruption of the Schlemm's canal and trabecular meshwork which facilitates the drainage of the aqueous humor. Its one main advantage is that it can be performed even if the cornea is cloudy (as in the case in childhood glaucoma). It is worth noticing that gonioscopy-assisted transluminal trabeculotomy is one of the trabecular-targeted MIGS techniques [30, 38-39].

Goniotomy is a procedure consisting of an incision of the trabeculum under the control of a gonioscopic lens. The main condition for performing goniotomy is that the cornea needs to be clear. Goniotomy is one of several methods used in primary congenital glaucoma treatment [40-41].

Implantation of glaucoma drainage devices (GDD) is indicated particularly for more severe cases or in the pediatric population. In adults, indications include excessive conjunctival scarring that diminishes the success of re-operations, abnormalities of the iridocorneal angle, neovascular glaucoma or presence of corneal grafts [42]. In children, GDDs are primarily used as reoperation after failed goniotomy or trabeculotomy and rarely as a first-line treatment in high-risk cases (e.g. aniridia, phakomatosis or aphakic glaucoma) [43]. GDDs were designed to overcome two problems with the trabeculectomy – to prevent the closure of the fistula diverting AH from the anterior chamber to the subconjunctival space (that is done with a silicone tube inserted into the anterior chamber and extended to the equatorial region of the eye) and to prevent failure of a filtering bleb because of conjunctival scarring to the sclera (this is done with an external plate that maintains potential space with a material that the conjuncti-

va cannot scar to and allows the creation of a capsule which is permeable for AH). There are non-valved implants such as Molteno or Baerveldt implants and valved implants such as Ahmed implants. Both types of implants (valved and non-valved) show significant IOP reduction, however the Ahmed implant (valved) reduces IOP less effectively, causing a greater need for glaucoma medications and a higher failure rate than the Baerveldt implant (non-valved) [44-47]. To decrease the risk of complications new GDDs are developed, e.g. the Paul Glaucoma Implant [28, 48-49].

The non-penetrating glaucoma surgery (NPGS) includes viscocanalostomy, canaloplasty, CO2 laser-assisted sclerectomy surgery and deep sclerectomy. These alternatives to traditional surgical procedures cause fewer complications, albeit they are demanding and the outcome depends on the operator's skills [50]. Deep sclerectomy is a relatively widely used NPGS method [51]. It involves removing the juxtacanalicular trabecula and the endothelium of Schlemm's canal (both have high resistance to AH outflow) with preservation of the thin trabeculo-Descement's membrane which allows permeating of AH [51-53]. Thereafter, AH can accumulate in a space within the sclera and eventually be drained through the subconjunctival space [53]. As a result, deep sclerotomy is an effective IOP-reducing operation for patients with open-angle glaucoma and can also be a treatment option for primary congenital glaucoma [51, 54].

Neuroprotection

Among various factors that significantly contribute to the pathogenesis of glaucoma, the role of oxidative stress, neuroinflammation and excitotoxicity is increasingly emphasized [55-56]. The excess of reactive oxygen species (ROS) damages the DNA, proteins, and lipids [57]. Research has shown that blood and aqueous humor levels of oxidative stress-related molecular biomarkers are greatly higher in samples taken from patients with developed glaucoma in comparison to healthy individuals [55, 58]. Inflammatory status is significantly changed as well. Dynamically elevating levels of various cytokines are observed [55, 59]. The use of substances with antioxidant and anti-inflammatory properties seems to be a reasonable solution for supporting glaucoma therapy. However, any therapeutic agents have not been explicitly approved for neuroprotection in glaucoma patients yet [8]. Many studies point to the antioxidant, anti-inflammatory and anti-apoptotic properties of *Ginkgo biloba*, *Lycium barbarum*, *Diospyros kaki*, *Tripterygium wilfordii*, saffron, curcumin, ginger, citicoline, caffeine, anthocyanin, coenzyme Q10, vitamins B3, D, E [55, 57, 60]. The results are conflicting on whether these substances have a clinically significant effect [57, 61]. Baicalein, forskolin, marijuana, ginsenoside, resveratrol and hesperidin are the other numerous natural substances, whose specific capability for lowering the intraocular pressure has been verified [55].

The use of marijuana for medical purposes including glaucoma treatment, is both interesting and controversial. In the 1970s-1980s of the XX century a number of studies were carried out to prove that the main psychoactive ingredient of cannabis, Δ-9-tetrahydrocannabinol (Δ^9-THC, commonly known as THC) is responsible for the IOP-lowering effect. Regardless of the route of THC administration (oral, intravenous, inhalation), a decrease in IOP was observed among people with and without glaucoma. Other classic cannabinoids (e.g. nabilone, Δ-8-tetrahydrocannabinol (Δ^8-THC), cannabinol, cannabidiol) and some THC metabolites have a similar effect on IOP [62-65]. Marijuana inhalation caused a reduction in IOP of patients with glaucoma within 30 minutes of administration and this effect lasted for approximately 4 hours [55]. Moreover, antioxidant and neuroprotective properties of cannabinoids have been reported [62]. In contrast, other studies describe the neurotoxicity of cannabis. They suggest that THC use is associated with increased neuronal background noise in the retina which leads to the altered neurotransmitter release [64, 66].

Marijuana's cardiovascular and neurological effects are also observed and may theoretically reduce the beneficial effect of lowering IOP by reducing ocular blood flow. The analyzed literature presents many disadvantages of cannabinoid use: very short duration of action, lack of evidence of a beneficial effect on the course of glaucoma, adverse effects (systemic and psychotropic) and the addiction potential. Current literature is consistent that evidence-based medicine does not explicitly recommend cannabis in any form of glaucoma treatment [66].

Hyperactivity of N-methyl-D-aspartic acid receptors (NMDAR) leads to the increased level of intracellular calcium, resulting in the damage of the plasma membrane, cytoskeleton, DNA and other cellular components. This process (referred to as excitotoxicity) affects the retinal ganglion cells, causing pathological changes co-responsible for the development of glaucoma [55-57]. Following that direction, NMDAR inhibitors and calcium channel blockers could potentially delay glaucoma progression, however this assumption has not been confirmed in randomized controlled trials among glaucoma patients, studying the utility of memantine (an NMDAR blocker commonly prescribed in Alzheimer's disease) [57, 67-68]. Nevertheless, in a placebo-controlled study on nilvadipine administered to patients with POAG for 3 years, Koseki et al. reported slowed visual field progression [69].

Wan et al. surveyed more than 1500 Canadian patients diagnosed with glaucoma and reported that almost 11% of them applied complementary and alternative medicine methods [70]. It should be clearly emphasized that reliable

research is necessary to determine the effects and safety of using those substances for medical purposes.

Vascular medications – neovascular glaucoma

Neovascular glaucoma (NVG), a type of secondary angle-closure glaucoma, characterized by intraocular neovascularization of the iris and/or anterior chamber angle, as well as increased IOP. Any disorder related to retinal ischemia (e.g. retinal venous obstructive disease, diabetic retinopathy, carotid artery obstructive disease, central retinal artery obstruction, ocular ischemic syndrome, rhegmatogenous retinal detachment, uveitis) may cause NVG [71]. The prolonged and intensified neovascularization and myofibroblast activity leads to the peripheral anterior synechiae and disruption of AH filtration, increasing IOP and a risk of glaucoma development. Panretinal photocoagulation is considered the gold standard therapy for pathological changes of the NVG. Positive effects of that procedure have been reported in many studies [71-73]. Alternatively to laser therapy, locally increased amounts of proteins involved in the neovascularization process might become a target for the NVG treatment. Therapy using anti-VEGF agents is being considered [71]. Studies on animal models document a rapid decrease in the intensity of anterior chamber neovascularization after the intravitreal injections of anti-VEGF antibodies: bevacizumab and ranibizumab [72, 74]. Unfortunately, these molecules do not have a high binding affinity to all VEGF isoforms and in consequence they are not an effective long-term solution. Aflibercept binds and influences multiple vascular growth factor isoforms, has a strong and long-standing biological effect [75]. A prospective case series revealed a rapid regression of early stages of iris and angle neovascularization in all included patients after an aflibercept injection [76]. Unfortunately, no guidelines for using intravitreal injections of anti-VEGF agents have been published, thus they remain as off-label methods [71]. A combined therapy based on the anti-VEGF proteins and the panretinal photocoagulation may be a treatment option [71]. A preoperative intravitreal injection with bevacizumab may reduce the risk of bleeding, inflammation and fibrosis after a trabeculectomy [77]. The same procedure resulted in greater IOP reduction and decreased incidence of complications after the GDD surgery [78]. Researchers wonder if a modification of ocular blood flow might play any role in effective glaucoma therapy [67]. A trial focused on dronabinol (a synthetic THC agent) investigated whether its oral administration affects the retinal vessel diameter, retinal oxygen saturation and retinal blood velocity, although the data have not been published yet [79].

Statins

Statins are commonly prescribed to patients with hyperlipidemia, however, they are of interest in glaucoma prevention and therapy [80]. Statins show wide pleiotropic effects whose molecular basis has not been precisely described [81]. They protect the retinal ganglion cells, probably due to their part in the inhibition of isoprenylation process, immunomodulation and decrease in the amount of glutamate [82]. Moreover, they activate the endothelial NOS and as a result, the retinal and choroidal blood flow improves, which results in a decreased IOP. Regulation of myosin II ATPase activity leads to a streamlined aqueous humor outflow in the iridocorneal angle [83].

Stein et al. reported a significant protective effect of 2 years of statin use. It is described as the 8% decreased risk of developing OAG in patients with hyperlipidemia treated with statins, compared to the individuals with hyperlipidemia who did not take them. The hypothesis is that statins inhibit glaucoma progression more effectively in the early stages of the disease.

A retrospective analysis of patients of the Erlanger Glaucoma Registry revealed that long-term treatment with statins, especially combined with acetylsalicylic acid correlated with a significantly reduced risk of glaucoma development and progression [84]. These results correspond to a prospective population-based cohort study done in the Netherlands which shows that long-term use (≥ 2 years) of statins results in reduced risk of OAG [85]. However, other studies did not confirm a significant relationship between statin use and the incidence and progression of glaucoma [81, 86]. That justifies further research to resolve this issue explicitly.

Conclusion

This review aimed to present current therapies for patients with glaucoma. It illustrates that the therapeutic choices in glaucoma go far beyond the well-known topical eye drops. What matters is that treatment must be individualized for every clinical patient, particularly taking into account the type of glaucoma and the patient's condition. Minimally invasive methods, GDD implants, laser and surgical therapies are commonly chosen solutions. We also pointed out less-known and controversial methods such as neuroprotection and the role of statins. The cited literature shows contradictory results whether these factors play any beneficial role in the glaucoma therapy. Nevertheless, some of the results were promising and justify further research on this topic.

Conflict of interest

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