

LEKARZ WOJSKOWY

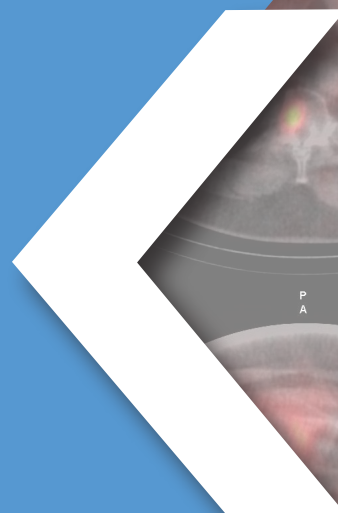
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- Intestinal parasitic infections among Ukrainian child war refugees living in Warsaw
- Analyzing the differences in concentration of anti-SARS-CoV-2 antibodies during COVID-19 depending on severity of the disease, sex, age and vaccination status
- Dyslipidaemias in children
- Epistaxis as a serious complication of high flow nasal cannula



**WOJSKOWY
INSTYTUT MEDYCZNY
PAŃSTWOWY INSTYTUT BADAWCZY**

Informacje dla autorów

Informacje ogólne

„Lekarz Wojskowy” jest czasopismem ukazującym się nieprzerwanie od 1920 r., obecnie jako kwartalnik wydawany przez Wojskowy Instytut Medyczny w Warszawie.

1. „Lekarz Wojskowy” zamieszcza prace oryginalne (doświadczalne i kliniczne), prace poglądowe, doniesienia dotyczące zagadnień wojskowych, opracowania deontologiczne, opracowania ciekawych przypadków klinicznych, artykuły z historii medycyny, prace dotyczące aspektów prawa medycznego, opisy wyników racjonalizatorskich, wspomnienia pośmiertne, listy do Redakcji, oceny książek, streszczenia (przeglądy) artykułów z czasopism zagranicznych, szczególnie dotyczących wojskowej służby zdrowia, sprawozdania ze zjazdów i konferencji naukowych, komunikaty o zjazdach. Publikacja oryginalna może mieć także formę krótkiego doniesienia wstępnego.
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Książki:
Rudziński E. *Alergia na leki: z uwzględnieniem odczynów anafaktycznych i idiosynkrazji*. Lublin, Wydawnictwo Czelej, 2002
Rozdziały książki:
Wantz GE. Groin hernia. In: Cameron JJ, ed. *Current surgical therapy*. St Louis, Mosby, 1998: 557–561
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 - 2) „Dobre praktyki w procedurach recenzyjnych w nauce” (opracowane przez Zespół ds. Etyki w Nauce, który doradzał Ministrowi Nauki i Szkolnictwa Wyższego w latach 2009–2010);
 - 3) „Rzetelność w badaniach naukowych oraz poszanowanie własności intelektualnej” (Warszawa, 2012, MNiSW).
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 - 6) zapewnia profesjonalny proces wydawniczy;
 - 7) zapewnia poufność i bezpieczeństwo przetwarzania danych osobowych zgodnie z obowiązującymi przepisami (m.in. RODC).

Information for the authors

General information

“Military Physician” has been published continuously since 1920, currently as a quarterly of the Military Institute of Medicine in Warsaw, Poland.

1. “Military Physician” publishes original (experimental and clinical) articles, reviews, reports on military issues, deontological papers, interesting case reports, articles on the history of medicine, descriptions of rationalisation results, posthumous memoirs, letters to the editor, book reviews, article (reviews) summaries from international journals particularly on military health service, reports on meetings and scientific conferences, and announcements of events. An original publication may also have the form of a short temporary report.
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- Books:
Rudziński E. *Alergia na leki: z uwzględnieniem odczynów anafaktycznych i idiosynkrazji*. Lublin, Wydawnictwo Czelej, 2002
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1. The journal “Lekarz Wojskowy” applies principles of publication ethics aimed at preventing unfair publication practices.
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3. The editorial board of “Lekarz Wojskowy” in particular:
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 - b) in justified cases, immediately inform the relevant scientific institutions, as well as the appropriate law enforcement authorities about these practices;
 - 6) ensure a professional publishing process;
 - 7) ensure confidentiality and security of personal data processing in accordance with applicable regulations (including GDPR).



■ Letter from the Editor-in-Chief

Dear Readers,

The holidays have ended, and we are beginning the new academic year, 2024/2025.

During the past few months, we have been diligently working on the new issue of “Military Physician” for you. Traditionally, it includes contributions from colleagues at various centres, both within Poland and internationally, which is crucial for both the journal and the editorial team.

In the latest edition of “Military Physician”, we feature two especially noteworthy articles: one addressing lipid disorders in children and another exploring the applications of whole-body cryotherapy in contemporary medical practice. Among the original research articles, we present studies assessing the risk of gastrointestinal parasitic diseases and examining SARS-CoV-2 antibody levels across various groups of individuals affected by COVID-19. We also recommend exploring a series of interesting case reports.

In response to the inquiries we have received, I would like to highlight that “Military Physician”, as a scientific journal, focuses on publishing scholarly works within the medical field. This includes research articles, educational pieces, information about scientific conferences, and contributions to the history of medicine, all adhering to the standards of scientific writing. Submissions that fall outside this scope are not considered for publication.

I am confident you will find this issue both informative and engaging.

I am looking forward to our continued cooperation.

A handwritten signature in blue ink, appearing to read 'B. Kalicki'.

Prof. Bolesław Kalicki, MD, PhD



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APPLICATION OF THERMOGRAPHY IN MEDICINE. PART II

Zastosowanie termografii w medycynie.
Część II



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Abstract

The first part of the paper presented the physical basis of infrared thermography and thermal imaging cameras (detectors) using the detection of infrared radiation to identify temperature changes in various parts of the human body, which makes infrared thermography useful in complementary diagnosis of diseases in many fields of medicine, such as angiology, internal medicine, aesthetic and reconstructive surgery (as described in the first part of the article), as well as in gynecology and obstetrics, cardiology and heart surgery, oncology, orthopedics, pediatrics, rheumatology, dentistry and urology (as described in this part of the article). Infrared thermography is a promising adjunctive diagnostic method. However, it has both advantages (non-invasiveness, short performance time, ability to generate images of the entire body, simultaneous detection of health problems and subclinical diagnosis), as well as disadvantages (possible impact of external factors, such as changes in ambient temperature, humidity and air movement, on the

Streszczenie

W pierwszej części artykułu przedstawiono podstawy fizyczne termografii oraz kamer termowizyjnych (detektorów), wykorzystujących detekcję promieniowania cieplnego, które umożliwiają wykrycie zmiany temperatur w różnych częściach ciała ludzkiego, dzięki czemu termografia znajduje zastosowanie w diagnostyce uzupełniającej chorób w wielu dziedzinach medycyny: angiologii, chorobach wewnętrznych, chirurgii estetycznej i rekonstrukcyjnej (co opisano w pierwszej części artykułu), a także w ginekologii i położnictwie, kardiologii i kardiochirurgii, onkologii, ortopedii, pediatrii, reumatologii, stomatologii i urologii (co przedstawiono w niniejszej, drugiej części artykułu). Termografia jest obiecującą, uzupełniającą metodą diagnostyczną. Ma zarówno zalety (bezinwazyjność, szybkość wykonania, możliwość obrazowania całego ciała i jednoczesnego wykrycia wielu problemów zdrowotnych oraz diagnozowanie na etapie subklinicznym), jak i wady (wrażliwość pomiaru na czynniki zewnętrzne, takie jak zmiany temperatury otoczenia, wilgotność i ruch powietrza), o których należy pamiętać podczas jej stosowania.

Keywords: oncology; orthopedics; thermography; gynecology and obstetrics; cardiology and cardiac surgery

Słowa kluczowe: onkologia; ortopedia; termografia; ginekologia i położnictwo; kardiologia i kardiochirurgia

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Introduction

The aim of this paper is to present the current knowledge on the applicability of thermography in various medical fields. The first part of this article discussed the physical aspects of infrared thermography (IRT) and thermal imaging cameras (detectors) using infrared (IR) detection, which make it possible to identify temperature changes in different parts of the human body, making IRT applicable for complementary diagnosis of disorders in many medical fields such as angiology, internal medicine, cosmetic and reconstructive surgery (as described in the first part of the paper), as well as gynaecology and obstetrics, cardiology and cardiac surgery, oncology, orthopaedics, paediatrics, rheumatology, dentistry and urology (as presented in this part of the paper)

Thermography in gynaecology and obstetrics

In gynaecology, IRT is used during hysterectomy (performed for oncological reasons) to differentiate anatomical structures (e.g., the ureter and the ostiomeatal complex or the iliac vessels and the ureter), the course and appearance of which may have been altered by the cancerous process or endometriosis [1].

In obstetrics, the method is used to monitor caesarean section wounds for early [2] and late infections, which is particularly important in obese women due to poor wound healing [3]. Additionally, IRT has been used since the 1990s to assess breast temperature during breastfeeding, both in the prevention of mastitis (screening) and to monitor the healing process and treatment efficacy (e.g., the use of ultrasound) [4], as well as in the diagnosis of mastitis in newborns and pubertal girls [5].

Thermography in cardiology and cardiac surgery

In cardiology, intravascular thermography allows for detecting and localising atherosclerotic plaques (unstable ones in particular) in the coronary arteries (the hypothesis of plaque formation is based on the initiation of local, active inflammation, and thus a rise in temperature, which can be detected with a thermal imaging camera) [6].

IRT additionally allows for:

- minimising the risk of thermal oesophageal damage during ablation in atrial fibrillation (rapid detection of critical temperature) [7];
- detecting even a slight decrease in chest wall perfusion after coronary artery bypass grafting (CABG) for ischemic heart disease, and preventing surgical site infection [8];
- diagnosing rare type 1 complex regional pain syndrome (CRPS) after percutaneous coronary intervention (by detecting temperature difference in both forearms) [9].

Thermography in oncology

IRT is a useful tool in oncology for monitoring the risk of radiation dermatitis following radiation therapy for breast cancer in patients after mastectomy and sparing procedures (skin temperature changes are measured at different intervals) [10].

Thermography has been also discussed as a potential tool for detecting and identifying:

- nodular lesions of the breast (both benign and malignant), as an alternative to mammography [11];
- thyroid nodules, including preliminary verification of their malignancy (malignant lesions have a higher temperature than benign ones) [12];
- various types of cancer, malignant and benign skin cancers [13];
- intraocular tumours, including treatment efficacy monitoring in intraocular melanoma by detecting regression (decrease in eye temperature) [14].

Thermography in orthopaedics

IRT is used in orthopaedics:

- for rapid screening diagnosis of bone fractures (hand, foot, collarbone, forearm), in the emergency setting [15];
- as a complementary investigation (in addition to EMG and nerve conduction testing) in the diagnosis of carpal tunnel syndrome (reduced palmar and dorsal temperature in the affected hand) [16];
- in the assessment of patients at risk of Sudeck's syndrome (sympathetic algodystrophy); importantly, across all three phases of the development of this disorder (reduced temperature of the affected limb, delayed temperature rise following cold stimulation) [17];
- for monitoring temperature during orthopaedic surgeries (overheating leads to necrosis and subsequent bone resorption), which allows for modifying the design of surgical instruments and techniques [18];
- for early detection of postoperative complications, such as infections, which are a major problem in hip and knee replacement [19].

Thermography in paediatrics

As a non-invasive and rapid tool, IRT is a valuable diagnostic complement in many areas of paediatrics:

- in paediatric ophthalmology and allergology (increased temperature is observed after intranasal application of nut protein spray in allergic patients) [20], as well as in juvenile arthritis (mainly of the ankle) [21];
- in screening for type I diabetes mellitus (lower skin temperature on IRT after cold stress test in children with diabetes has been noted, although in clinical evaluation, impaired vascular perfusion is not apparent until many years after the disease onset) [22];
- for fracture risk assessment or fracture screening [15];
- for evaluating the healing of burns and wounds (including post-amputation), as well as for deciding on the extent of amputation [23];
- for monitoring newborns (including preterm infants) at risk for respiratory conditions (based on aberrant temperature changes seen on IRT associated with airflow delay between the chest and abdomen [24]) and necrotizing enterocolitis (based on abdominal temperature differences) [25];
- In paediatric neurology (monitoring of valvular function in children with hydrocephalus, screening for attention deficit hyperactivity disorder) [20].

Thermography in rheumatology

Since joints involved by active inflammation show an increased warmth compared to joints in remission (although the difference is small, and for this reason ultrasound is the most optimal tool [26]), IRT is used in rheumatology to diagnose arthritis (including rheumatoid and juvenile arthritis [21]).

In addition, IRT is used for assessing the Raynaud's phenomenon, as the surface temperature of the hands/fingers is a measure of the overall capillary blood flow [27], which allows to confirm or exclude the diagnosis, and, with additional cold/warm stress, allows to distinguish between primary and secondary conditions, and contributes to the objectivity of patient assessment [28]. This method is also used in the treatment of systemic scleroderma to assess disease activity and response to treatment [27].

Thermography in dentistry

IRT is used in dentistry:

- for the diagnosis of periapical inflammatory lesions, acute pulpitis with apical periodontitis, as well as acute and chronic periapical abscess (all in the pre-clinical phase, which allows rapid diagnosis and treatment) [29];
- in implantology (elevated bone temperature when drilling for an implant is a negative prognostic factor as it disrupts the physiological balance of proteins in bone cells [30]);
- in dental surgery (for temperature monitoring during the application of different types of techniques during osteotomy: contact and non-contact Er:YAG laser treatment, piezoelectric surgery and surgical drill, to assess for potential tissue overheating, which is a negative prognostic factor [31]);
- endodontics (for assessing root temperature when using different filling techniques, assessing the volume of endodontic filling materials and potential empty spaces, which are a negative prognostic factor [32]);
- in oral inflammation (e.g., caused by wearing dentures, also as a screening and prognostic test [33]).

Thermography in urology

IRT is used in urology to monitor genitourinary inflammation, prostatitis, testicular inflammation, bladder and urinary tract inflammation [34], as well as to diagnose altered seminal vasculature in young men [35]. IRT is also used to assess renal blood flow, which is particularly useful in patients with diabetes mellitus or heart disease, and during transplantation procedures [36].

Conclusions

Thermal imaging is a promising complementary diagnostic approach used in many fields of medicine. Like any other diagnostic or therapeutic tool, IRT has both advantages and disadvantages. Advantages include non-invasiveness, short duration, the possibility of full-body imaging and simultaneously detecting multiple health problems, and, particularly importantly, the possibility to diagnose a given disorder at its subclinical stage, al-

lowing for rapid implementation of effective treatment. Disadvantages that should be considered when using this method include the possible impact of external factors on the measurement (such as changes in ambient temperature, humidity and air movement), poor resolution, especially in the case of cheaper, low-class systems, which makes interpretation of the result difficult, as well as the high price of high-end devices.

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DYSLIPIDAEMIAS IN CHILDREN

Zaburzenia lipidowe u dzieci



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Abstract

Lipid disorders (dyslipidemias) in children have so far been associated with genetically determined lipid disorders (such as familial hypercholesterolemia). Due to unfavorable lifestyle changes in recent years, in addition to congenital forms of dyslipidemia, acquired, environmentally determined lipid disorders are increasingly being found in children, which carries the risk of developing atherosclerosis and future cardiovascular incidents. In 2021, Polish recommendations for diagnosing and treating dyslipidemia were published, for the first time including the pediatric population. The article discusses lipid metabolism in humans and the norms of lipid indices in developmental age. In addition, the most common genetically determined dyslipidemias are presented, as well as forms secondary to kidney disease and diabetes. In addition, the article discusses treatment options for lipid disorders in developmental age. All children with dyslipidemia require non-pharmacological management. The indications for implementing pharmacotherapy, the most commonly used drugs, dosage, and possible complications are also discussed. The use of statins in children is discussed in detail.

Streszczenie

Zaburzenia lipidowe (dyslipidemie) u dzieci były do tej pory kojarzone z uwarunkowaniami genetycznymi (np. rodzinną hipercholesterolemią). W ostatnich latach, ze względu na niekorzystne zmiany trybu życia, poza wrodzonymi postaciami dyslipidemii coraz częściej stwierdza się już u dzieci nabyte, uwarunkowane środowiskowo zaburzenia lipidowe, co niesie za sobą ryzyko rozwoju miażdżycy, a w przyszłości – wystąpienia incydentów sercowo-naczyniowych. W roku 2021 ukazały się polskie rekomendacje dotyczące diagnostyki i leczenia dyslipidemii, w których po raz pierwszy tak szeroko omówiono także populację dziecięcą. W artykule przedstawiono metabolizm lipidów i normy wskaźników lipidowych w wieku rozwojowym. Ponadto opisano najczęstsze uwarunkowane genetycznie dyslipidemie, a także postacie wtórne do chorób nerek i cukrzycy. Omówiono też sposoby leczenia zaburzeń lipidowych w wieku rozwojowym. Wszystkie dzieci z dyslipidemią wymagają postępowania nefarmakologicznego. Przedstawiono wskazania do wdrożenia farmakoterapii, najczęściej stosowane leki, dawkowanie i możliwe powikłania. Szczegółowo omówiono zasady stosowania statyn u dzieci.

Keywords: children; lipids; statins; lipid disorders; non-pharmacological treatment

Słowa kluczowe: dzieci; lipidy; statyny; zaburzenia lipidowe; postępowanie nefarmakologiczne

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Introduction

The problem of lipid disorders in the paediatric population usually arises in the context of inherited dyslipidaemias and the increasing prevalence of obesity among children and adolescents. Due to the underestimation of the problem in this age group and the fact that a large proportion of lipid-lowering agents have not been approved for paediatric patients, paediatricians have long faced the lack of clear guidelines for the management of lipid disorders in children. In recent years, the problem of dyslipidaemia has been increasingly raised by researchers, redefining the magnitude and severity of its consequences, as well as seeking the optimal therapeutic pathways for both adult and paediatric patients. This paper discusses lipid disorders in the paediatric population and summarises the current knowledge and guidelines in this field.

Characteristics of lipids

Lipids (fats) are a heterogeneous group of chemical compounds sharing two properties, i.e. insolubility in water and solubility in non-polar solvents. Fats play many important roles in the body. They are the most calorie-dense food component, providing about 9 kcal in 1 g (compared to 4 kcal in 1 g for protein or carbohydrates). They are a solvent for vitamins (mainly A, D, E, K). Lipids also act as a thermal insulator, making up the subcutaneous fat tissue and surrounding internal organs, as well as an electrical insulator, as the main component of the myelin sheath. Fats are also an essential component of the cell membrane and enable the transport of other lipids in the plasma. Furthermore, lipids are substrates in the synthesis of other biologically important substances, such as steroid hormones [1]. All these functions require both endogenous and exogenous lipid supply. Acetyl-coenzyme A (acetyl-CoA), which is obtained from carbohydrates and can be converted to free fatty acids through liponeogenesis after excess energy intake with food, is the main endogenous source of lipids. Liponeogenesis and lipogenesis, i.e. conversion of free fatty acids into triglycerides, are stimulated under physiological conditions by, among other things, hyperinsulinemia. The reverse process of extracting energy from free fatty acids takes place through β -oxidation in situations of energy deficiency, for example, under fasting conditions or after stress-induced catecholamine release. Animal or plant triglycerides, sterols and membrane phospholipids, ingested with food and broken down to bioavailable forms by enzymes (salivary and gastric lipase, bile, pancreatic lipase, phospholipase, carboxyl esterase, intestinal lipase and alkaline phosphatase) represent external sources. Short- to medium-chain fatty acids (up to 12 carbon atoms) and glycerol are absorbed in the duodenum and enter the liver via the hepatic vein, while long-chain fatty acids, cholesterol, monoglycerides, phospholipids and glycerol, broken down in the distal small bowel, reach the enterocytes, where two important processes take place, i.e., the resynthesis of triglycerides from free fatty acids and glycerol, and the esterification of cholesterol by acyl-coenzyme A (CoA):cholesterol acyltransferases (ACATs). Triglycerides additionally require the attachment of apolipoprotein (apo) B-48 molecules,

followed by apoA-I and apoC-II, forming prechylomicrons, respectively. This results in the final assembly of lipids for transport to the liver, where they can undergo further transformation, or to target tissues, where they are metabolised. Triglycerides cannot freely pass from the plasma directly into tissues, but must be broken down by lipoprotein lipase (LPL), which allows their trans-membrane transport. After reaching the target site, the released fatty acids can be used as energy sources or substrates for the synthesis of new triglycerides, deposited in the cytosol, or substrates for cell membrane synthesis [2].

Plasma lipid transport

Cholesterol esters (36%), phospholipids (30%), triglycerides (16%), cholesterol (14%) and non-esterified free fatty acids (4%) are the main forms of lipids found in the plasma. Of these, only the latter are characterised by polarity and, as such, can be transported when bound to albumin. In order for the remaining groups, i.e. non-polar triglycerides and cholesterol esters, as well as amphipathic (i.e. both polar and nonpolar) phospholipid and cholesterol molecules, to be transported in the plasma, they require the attachment of appropriate proteins or, additionally, prior aggregation with each other, i.e. non-polar molecules with amphipathic ones, to form water-soluble lipoprotein molecules. This process enables normal lipid metabolism, in which fats absorbed in enterocytes or synthesised in the liver can, in the form of chylomicrons and very-low-density lipoproteins (VLDL), respectively, reach the appropriate tissues. The extent to which lipoproteins participate in the reverse process, i.e. the "recovery" of lipids stored in adipose tissue, is much more limited, since it is mainly the transport of free fatty acids (bound to albumin), but they play a key role in the transport of cholesterol. Impaired lipoprotein metabolism leads to hypolipoproteinemias or hyperlipoproteinemias, which will be discussed in more detail later in the paper [3]. Lipoproteins differ in their density, depending the ratio of protein to lipid content in the molecule, while the type of these proteins (apolipoproteins) determines the function of a given lipoprotein group. Four classes of the most functionally and diagnostically important lipoproteins may be distinguished: ultra-low-density lipoproteins (ULD), also known as chylomicrons, derived from intestinal absorption of triglycerides and other lipids; very-low-density lipoproteins (VLDL), formed in the liver to carry triglycerides; low-density lipoproteins (LDL), which are the primary carriers of cholesterol in peripheral tissues; and high-density lipoproteins (HDL), responsible for reverse cholesterol transport (from peripheral tissues to the liver) and involved in the metabolism of VLDL and chylomicrons [2, 4]. These apolipoproteins have many functions in addition to being a component of lipoproteins. They serve as cofactors for enzymes, such as apoC-II for lipoprotein lipase or apoA-1 for lecithin-cholesterol acyltransferase (LCAT), i.e. functional plasma equivalent of intracellular ACAT; they can be enzyme inhibitors, such as apoA-II and apoC-III for LPL, apoC-I for cholesteryl ester transfer protein (CETP); and are ligands for lipoprotein receptors in tissues, such as apoB-100 and apoE for the LDL receptor (LDL-R), apoE for the LDL receptor-related protein (LRP), and apoA-I for the HDL receptor (HDL-R) [5].

Table 1. Reference lipid parameters in children according to [6] in our own modification

	Range of a given fraction [mg/dL]		
	Normal	Borderline	High/Low
Total cholesterol	<170	170-199	≥200
LDL	<110	110-129	≥130
Non-LDL	<120	120-144	≥145
Triglycerides			
0-9 years	<75	75-99	≥100
10-19 years	<90	90-129	≥130
HDL	>45	40-45	<40
Apolipoprotein B	<90	90-109	≥110
Apolipoprotein A-1	>120	115-120	<115

HDL - high density lipoproteins; LDL - low density lipoproteins

Dyslipidaemias in children

Dyslipidaemia is a general medical term used to describe abnormal blood lipid levels. It includes abnormalities related not only to cholesterol, but also to triglycerides and other lipids. Three ranges for different lipid fractions, i.e., normal, borderline and too high/too low, which are an indicator of the type of dyslipidaemia, have been distinguished in children [6]. Reference values proposed in American guidelines are summarised in table 1.

Dyslipidaemia is classified as secondary (caused by other diseases or conditions) or primary (caused by genetic or environmental factors). There are two main categories of hereditary dyslipidaemias: hyperlipidaemias and hypolipoproteinemias.

To date, the greatest emphasis in the diagnosis of lipid disorders in children has been placed on patients presenting with various forms of familial hypercholesterolemia (FH). It is one of the most common hereditary lipid disorders, characterised by elevated LDL cholesterol levels. The disorder is caused by reduced production of LDL-R due to mutations in genes responsible for cholesterol metabolism, such as *LDL-R* or *PCSK9*, which encodes proprotein convertase subtilisin/kexin type 9 (a protein that regulates cholesterol levels by controlling the amount of LDL-R on the surface of hepatocytes). Children with FH are characterised by elevated LDL levels from birth and, if left untreated, they may be at risk for earlier cardiovascular incidents, which significantly worsens their quality of life and reduces their life expectancy. For this reason, methods for early diagnosis and treatment of FH in children, such as screening programmes, have long been known [7, 8]. However, although the best known and described, FH is not the most common type of hereditary hyperlipidaemia. Other disorders include familial combined hyperlipidaemia (FCH), familial dysbetalipoproteinemia and familial hypertriglyceridemia. The types and subtypes of hereditary hyperlipidaemias are summarised in table 2.

The second group of hereditary dyslipidaemias includes the aforementioned hypolipoproteinemias, which are disorders characterised by a decrease in one or more lipoprotein fractions. Most of them are rare disorders, and their symptoms are rather due to the deficiency of fat-soluble vitamins; for example, in chylomicronemia or abet-

alipoproteinemia characterised by an impaired transport of chylomicrons from enterocytes to the liver [9]. On the other hand, this category also includes familial deficiency of the above mentioned LCAT, a disorder with high mortality rates due to cholesterol deposition in tissues, including the kidneys, leading to their failure. This is due to the complete or partial absence of LCAT, which prevents efficient esterification of cholesterol and its removal from tissues by HDL [10]. Apolipoprotein B deficiency, which is categorised as a hypolipoproteinemia simply because apolipoprotein B is essential for the synthesis and stabilisation of lipoproteins, including LDL, and therefore its deficiency can impair their function, although the disorder itself progresses with elevated plasma LDL levels, its clinical manifestations are rather similar to those of hyperlipidaemia and it is treated in a similar manner, is an interesting example of another disorder in this group of dyslipidaemias. Selected hypolipoproteinemias are presented in table 3.

Until recently, mainly hereditary forms have been associated with the paediatric population due to strongly expressed symptoms often occurring in childhood, as well as serious complications, such as myocardial infarction or stroke, developing at a very young age. In recent years, however, attention has been drawn to the growing prevalence of primary dyslipidaemia, which is due to poor lifestyle rather than genetic factors, among children. Lipid metabolism disorders co-occur with excess body weight, which in turn results from poor physical activity and excess intake of calories, which cannot be utilised even despite the increased demand during development. The problem seems to be growing, with dyslipidaemia diagnosed in one in five children in some epidemiological studies [11, 12].

There are also secondary dyslipidaemias, which arise in the course of other disorders. Diabetes mellitus, in which hyperglycaemia occurs by various mechanisms, leading to increased triglyceride production, is an example. Diabetic patients may also present with decreased LPL activity, which inhibits triglyceride removal from the blood, as well as insulin resistance, increasing hepatic fatty acid synthesis, which results in hypertriglyceridemia [13]. Patients with diabetic kidney disease or other conditions causing renal damage may develop chronic kidney disease (CKD), which can also lead to dyslipidaemia. Loss

Table 2. Hereditary hyperlipidaemias

Type	Full name	Impairment	Elevated fraction	Primary symptoms	Treatment	Symptom onset
I	a Familial hyperchylomicronaemia/ Buerger-Grutz syndrome	↓ LPL	Chylomicrons	AP, lipemia retinalis, eruptive xanthomas, hepatosplenomegaly	Diet	Childhood (abdominal colic and eruptive xanthelasma)
	b Familial apolipoprotein C-II deficiency	Abnormal apoC2				
	c -	Plasma LPL inhibitor				
II	a Familial hypercholesterolemia	↓ LDL-R	LDL	Xanthelasma/ flat xanthelasma, <i>arcus senilis</i> , tendon xanthelasma	Ion exchange resins, statins, niacin	From birth
	b Familial combined hyperlipidaemia	↓ LDL-R ↑ apoB	LDL VLDL	-	Statins, niacin, fibrates	Childhood to adulthood
III	Familial dysbetalipoproteinemia	Impaired apoE2 synthesis	IDL	Nodular xanthelasma, palmar xanthelasma	Fibrates, statins	Typically 30–60 years of age
IV	Familial hypertriglyceridemia	↑ production VLDL ↓ elimination VLDL	VLDL	AP (with high TG levels)	Fibrates, niacin, statins	Adolescence
V	-	↑ production VLDL ↓ production LPL	VLDL chylomicrons	-	Niacin, fibrates	Childhood to adulthood

apo – apolipoprotein; IDL – intermediate-density lipoproteins; LDL – low-density lipoproteins; LDL-R – LDL receptor; LPL – lipoprotein lipase; HDL – high-density lipoproteins; AP – acute pancreatitis; VLDL – very-low-density lipoproteins

Table 3. Hereditary hypolipoproteinemias

Disorder	Mechanism	Fraction	Manifestations	Treatment
Familial lecithin cholesterol acyltransferase (LCAT) deficiency	↓ LCAT	↓ HDL ↑ LDL ↑ VLDL ↑ TG	Corneal opacity, renal failure, hepatic failure, anaemia, premature atherosclerosis (rare)	Diet, cornea transplant, dialysis
Tangier disease	<i>ABCA1</i> mutation	↓ HDL ↑ TG	Hepatosplenomegaly, peripheral neuropathies, corneal opacification, orange discoloured tonsils	Diet, niacin, gemfibrozil
Chylomicronaemia syndrome	<i>SAR1B</i> mutation	↓ LDL	Abdominal pain, diarrhoea, fatty stools, hepatomegaly, cardiomyopathy	Diet, vitamin supplementation
Abetalipoproteinemia	↓ apoB-48 ↓ apoB-100	↓ TG ↓ LDL ↓ VLDL ↓ chylomicrons	Steatorrhea, vitamin A, D, E, K deficiency, acanthocytosis, polyneuropathy, retinitis pigmentosa	Diet, vitamin supplementation
Apolipoprotein B deficiency	↓ apoB-100	↑ LDL	Xanthelasma/flat xanthelasma, <i>arcus senilis</i> , tendon xanthelasma	Niacin, statin, ezetimibe

apo – apolipoprotein; LCAT – lecithin-cholesterol acyltransferase; LDL – low-density lipoproteins; HDL – high-density lipoproteins; TG – triglycerides; VLDL – very-low-density lipoproteins

of filtration function, which prevents the kidneys from efficiently removing VLDL and chylomicrons, such as through reduced clearance and accumulation of apoC-III in the blood, is the main cause of dyslipidaemia in CKD and leads to inhibition of triglyceride breakdown by LPL in plasma [14]. Another reason is the reduced LCAT activity in CKD, especially in end-stage renal failure [15], which leads to decreased HDL, as in hereditary deficiency of this enzyme. It is these two fractions, namely HDL and

triglycerides, that are found at abnormal levels in CKD patients, while the LDL fraction generally remains within normal limits. Nephrotic syndrome, which is a disorder of the glomerular filtration barrier, is another nephrological condition typical of the developmental age. This disorder results in the loss of albumin in the urine and a compensatory overproduction of VLDL and LDL, although this view is questioned due to a lack of conclusive evidence from experimental studies [16]. In addition to albumin,

apolipoproteins, such as apoA-I and apo-II, which make up HDL particles, are also lost, which may reduce blood levels of this lipid fraction [17]. Nephrotic syndrome may be also associated with increased production of PCSK9, which increases LDL fraction [18].

Furthermore, dyslipidaemia may be induced by medications, such as non-selective beta-blockers, thiazide diuretics, mammalian target of rapamycin (mTOR) pathway inhibitors and neuroleptics, used in children [19].

The importance of dyslipidaemia

Atherosclerosis is the primary condition associated with elevated plasma LDL. Although the disorder mainly affects adults, especially those with multimorbidity, it is increasingly common in children, primarily due to the growing problem of poor nutrition and lack of physical activity, which, in addition to excess body weight, can also lead to hypercholesterolemia.

Atherosclerosis begins when the inner layer (endothelium) of the blood vessel is damaged. This can be caused by various factors, such as cigarette smoking, hypertension, diabetes or hyperlipidaemia.

Damaged endothelium secretes chemical factors such as adhesion molecules and cytokines that attract leukocytes to the site of damage. LDL can then pass through the damaged endothelium into the tunica media, where it is oxidized by free radicals, and thereby modified and transformed into the so-called damaged LDL. Such LDL particles are more likely to adhere to endothelial cells and monocytes, which are also attracted to the damaged tissue. Monocytes transform into macrophages, which take up the damaged LDL, but being unable to digest it, transform into foam cells, which accumulate and form an increasingly thick layer of atherosclerotic plaque. A growing atherosclerotic plaque narrows the lumen and increases its stiffness, which can eventually lead to serious hemodynamic complications, such as myocardial infarction or stroke [20, 21].

Hypertriglyceridemia, which often leads to acute pancreatitis, is another disorder that may develop in the course of dyslipidaemia. This occurs due to an excess of free fatty acids (released from triglycerides), which exceed the ability of plasma albumin to bind them and, after combining with calcium, may cause fat embolism in pancreatic blood vessels. This in turn leads to vascular damage, inflammation and, consequently, acute pancreatitis (AP) followed by many complications, mainly diabetes, but also infections and multiple organ dysfunction [22].

Treatment of dyslipidaemia in children

The 2021 guidelines for the diagnosis and treatment of lipid disorders, developed by many Polish scientific societies dealing with this issue, provided paediatricians with clear recommendations for the management of children with dyslipidaemia in their daily clinical practice [23]. This is the first comprehensive study in a relatively large group of patients, as until now familial hypercholesterolemia was the only lipid disorder with definite diagnostic and therapeutic recommendations [24].

Non-pharmacological treatment

All >2 year-olds with LDL cholesterol levels >100 mg/dL and/or increased triglycerides, defined as ≥ 100 mg/dL in children <10 years and ≥ 130 mg/dL in those 10–19 years of age, require education on the causes and consequences of dyslipidaemia, risk factors for cardiovascular disease, as well as the principles and importance of therapy. This should apply to both the patient and all family members. Lifestyle recommendations are similar to those for adults and include proper diet, increased physical activity and, consequently, normalisation of body weight. When used effectively, these measures do not cause major LDL reduction, but significantly reduce triglycerides and increase HDL [23].

Diet

Patients with increased LDL levels are recommended to limit total fat-derived energy intake to 30%, with saturated fats accounting for less than 7% and being replaced by unsaturated fats, and with recommended daily cholesterol intake < 200 mg. Furthermore, efforts should be made to increase the daily intake of dietary fibre to about 10 g at 5 years, 15 g at 10 years, and 20 g at 15 years, as well as to increase the proportion of marine fish (at least once or twice a week), vegetables, fruits, nuts and seeds, as well as plant sterols and stanols in the diet (to about 2 g per day). Patients with increased triglycerides are recommended to reduce the proportion of simple sugars in their diet in favour of fibre and complex sugars, as well as normalise their body weight. It is also advisable to limit food thermal processing techniques to grilling and water or steam cooking [25].

Physical activity

In children <2 years, the therapeutic goal should be to completely or partially reduce the screen time. For children >2 years of age, this time should be a maximum of 2 hours per day. Additionally, the recommended daily physical activity in this age range should be at least 90 minutes [26].

Stimulants

Underage patients who admit to alcohol and cigarette use should, like adults, be strongly advised to discontinue these stimulants. Alcohol cessation has a proven beneficial effect on triglyceride reduction [27], while discontinuing nicotine raises HDL levels [28].

Pharmacological treatment

If the aforementioned non-pharmacological recommendations do not bring the expected improvement after 6 months, pharmacotherapy should be initiated as part of primary prevention of cardiovascular disease (CVD). For this purpose, lipid testing should be performed in duplicate over a period of 2 weeks to 3 months, on an empty stomach. Also, risk factors for CVD should be assessed. If hypertriglyceridemia is diagnosed, the child should be referred to a specialist clinic for a detailed diagnosis of the cause. In the case of a plasma triglyceride level >500 mg/dL, pharmacotherapy should be initiated in

parallel with the referral for diagnosis as part of prevention of acute pancreatitis. Similar management is recommended when genetic hypertriglyceridemia is suspected. For this purpose, statins, fibrates and omega-3 fatty acids can be used in children.

Statins

Treatment with 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA) inhibitors, referred to as statins, should be considered in:

- children ≥ 10 years of age, without risk factors and with stable LDL levels > 190 mg/dL;
- children with at least one high-risk factor or at least two intermediate risk factors and with LDL > 160 mg/dL;
- children with diabetes or FH and LDL ≥ 130 mg/dL.

High-risk factors include hypertension requiring pharmacotherapy, renal failure, body mass index (BMI) > 97 th percentile, while intermediate-risk factors include hypertension not requiring pharmacotherapy, HDL levels < 40 mg/dL, BMI between the 95th and 97th percentile, chronic inflammatory disease (rheumatoid arthritis, systemic lupus erythematosus) and nephrotic syndrome.

Statin therapy can be prescribed by any doctor, without a specialist consultation, starting with the lowest available dose used once daily, in the evening. Statins are the drugs of first choice in the treatment of hypercholesterolemia. Atorvastatin and rosuvastatin are currently the most widely used treatments. In Poland, medicinal products containing rosuvastatin are registered for patients aged ≥ 6 years, while atorvastatin is approved for children 10 years of age and older. The activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum creatine kinase (CK) levels should be measured before initiating statin therapy. Treatment should not be commenced when the activity of any of these aminotransferases is at least 3 times the upper limit of normal (ULN) for age or CK is at least 4 times the ULN for age. Other criteria for discontinuing statin therapy include hypersensitivity to the drug, active liver disease, renal failure, severe infections, major trauma and surgery, severe metabolic or endocrine disorders, and uncontrolled epilepsy. The recommended daily doses of statins in children are 5–40 mg for atorvastatin, 5–20 mg for rosuvastatin, as well as 5–20 mg in children < 13 years and 40 mg in children < 18 years for pravastatin. The authors also report a recommended daily dose of simvastatin of 5–40 mg, while not recommending its use.

ALT activity should be measured in patients on statins who develop liver symptoms, such as abdominal pain, weakness or jaundice. If muscle symptoms occur, serum CK levels should be checked. Additionally, a lipid panel should be done 6 weeks after the onset of pharmacotherapy and after any treatment modification to monitor treatment goals. If an increased ALT activity of > 3 ULN is found, treatment should be discontinued or the dose reduced, while treatment can be continued if ALT activity is increased but remains at < 3 ULN, with repeated measurement in 4–6 weeks. Statin therapy should be discontinued if symptoms of myopathy confirmed by laboratory tests occur [23].

The therapeutic goal for statins in children is to reduce LDL below 130 mg/dL or by 30–50% from baseline. For children with diabetes, familial hypercholesterolemia or a family history of coronary artery disease diagnosed before the age of 40 years, the goal is to reduce LDL to < 100 mg/dL or by at least 50% from baseline. Once the therapeutic goal is achieved, lipids should be monitored 1–2 times a year [23, 29].

Other therapies

Co-administration of several lipid-lowering drugs, such as ezetimibe at a daily dose of 10 mg, but also mipomersen, alirocumab and evolocumab (PCSK9 inhibitors), can be considered in patients already put on statins (the authors of the recommendations do not mention the recommended daily doses in children). Given the limited data on the efficacy and safety of such management in children, the inclusion of additional treatments should be supervised by a specialist.

Conclusions

In addition to hereditary dyslipidaemias, acquired, environmentally determined lipid disorders are increasingly diagnosed already in childhood due to unfavourable lifestyle changes in recent years. Every family doctor and paediatrician should be able to correctly interpret a lipid panel in a child. The recommendations published in 2021 provide clear guidelines for the diagnosis and management of dyslipidaemias, also in children. Non-pharmacological approaches remain the cornerstone of the treatment of dyslipidaemia in the paediatric population. Pharmacological management (mainly statins) is used in selected cases clearly defined in the available recommendations.

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WHOLE BODY CRYOTHERAPY IN MODERN MEDICINE

Zastosowanie krioterapii ogólnoustrojowej
we współczesnej medycynie



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Abstract

20th century medicine saw the development of many physiotherapy fields. Among these, a new department called cryotherapy or cold treatment was created. This paper focuses on systemic cryotherapy, which is performed in a specially designed cryogenic chamber. Despite extensive literature on cryotherapy, the general indications mainly include pain and oedema reduction. Thus, they are often limited to rheumatologic diseases and osteoarthritis. Disability, joint pain and muscular atrophy, which occur at an increasingly young age, represent a civilization problem faced by societies suffering from physical activity deficit. Furthermore, disorders such as obesity and depression are on the rise. In both cases, the underlying cause can be traced to lifestyle changes. Inadequate diet and insufficient physical activity from an early age lead to the so-called lifestyle diseases at an increasingly early age. Whole body cryotherapy seems to be an ideal option for such patients as cold reduces pain that can occur even in fibromyalgia. This is confirmed by recent studies. Among other things, cryotherapy may be successfully used for chronic pain in patients with osteoarthritis, rheumatoid arthritis and other rheumatic diseases, as well as multiple sclerosis. In these patients, systemic cryotherapy may be the solution that not only reduces pain, but also has an anti-oedematous and anti-inflammatory effect.

Streszczenie

W medycynie XX w. nastąpił rozwój wielu dziedzin fizjoterapii. Powstał nowy dział o nazwie krioterapia, czyli leczenie zimnem. Praca dotyczy krioterapii ogólnoustrojowej, która przeprowadzana jest w specjalnej komorze kriogenicznej. Piśmiennictwo na temat krioterapii jest bardzo obszerne, jednak wskazania ogólne do zastosowania tej metody odnoszą się głównie do zmniejszenia dolegliwości bólowych i łagodzenia obrzęku, zatem często ograniczają się do chorób reumatologicznych i chorób zwyrodnieniowych stawów. Problemem cywilizacyjnym społeczeństwa cierpiącego na niedobór ruchu jest coraz wcześniej pojawiająca się niepełnosprawność, bóle stawów i zaniki mięśniowe. Mało tego, coraz częściej występują choroby takie jak otyłość i depresja. W obu przypadkach podłoża można doszukiwać się w zmianie stylu życia. Nieodpowiednia dieta i zbyt skąpa aktywność fizyczna już od najmłodszych lat są powodem występowania w coraz wcześniejszym wieku tzw. chorób cywilizacyjnych. Krioterapia ogólnoustrojowa wydaje się dla takich chorych idealną metodą terapii, gdyż zimno zmniejsza dolegliwości bólowe, które mogą występować nawet w fibromialgii, co potwierdzają najnowsze badania. Doskonale sprawdza się między innymi w chronicznych bólach, jakie towarzyszą pacjentom z chorobą zwyrodnieniową stawów, reumatoidalnym zapaleniem stawów i innymi chorobami reumatycznymi oraz stwardnieniem rozsianym. U tych chorych rozwiązaniem może stać się zastosowanie krioterapii ogólnoustrojowej, która nie tylko zmniejsza dolegliwości bólowe, ale również wykazuje działanie przeciwozpalne i przeciwzapalne.

Keywords: cryotherapy; whole body cryotherapy (WBC); cryochamber; cold therapy

Słowa kluczowe: krioterapia; krioterapia ogólnoustrojowa; kriokomora; terapia zimnem

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Introduction

20th century medicine witnessed the development of a new type of treatment called cryotherapy. The word is derived from Greek and means treatment with cold. Whole body cryotherapy (WBC) uses cold as a therapeutic agent. It causes constriction of blood vessels in the initial stage of cold exposure and their significant dilatation in the final stage of exposure. As a result, tissues are supplied with fresh blood. This is followed by an internal warming of the body, improved cell nutrition and oxygenation, as well as an acceleration of the metabolism. Cold has healing and rejuvenating properties.

The procedure, which involves whole-body exposure to very low temperatures ranging from -120°C to -180°C , is performed in a special cryogenic chamber and lasts approximately 2–3 minutes. The temperature of the skin and subcutaneous tissues drops in a controlled manner, producing a highly beneficial therapeutic effect. The treatment in the cryochamber is followed by systemic exercises under the guidance of a physiotherapist [1–3].

Historical background

Cold treatments were already used by the Egyptians about 2500 BC. It was in the 5th century BC that Hippocrates recommended hypothermia to reduce oedema, bleeding and pain. He also discovered the analgesic properties of cold [4]. Napoleonic surgeon Baron Dominique Jean Larrey observed during the Russian campaign that soldiers could have their limbs amputated with less pain and bleeding when previously placed in ice or snow.

The properties of ethylene chloride have been known since the first half of the 19th century. They were discovered in France in 1847 by Jean Pierre Florens, who applied the chemical compound topically. In 1866, ethylene chloride was used in aerosol form by Pierre Redard (Sweden) for general analgesia. To this day, it is still widely used in sports medicine as a pain reliever after injuries.

The beginning of modern cryogenics is marked by mastering gas liquefaction at the end of the 19th century. Physicists of that time, including Poles, liquefied oxygen, carbon dioxide, air and hydrogen. They also made it possible to produce these gas on an industrial scale and to utilise them to this day. These achievements contributed to the development of anaesthesiology and general cryotherapy.

In 1907, Whitehouse constructed a device to release liquid nitrogen vapour to treat superficial tumours and certain skin lesions.

The concept of cryotherapy as a stimulating application of cryogenic temperatures (below -100°C) over a short period of time (2–4 minutes) to elicit physiological systemic responses to cold, support primary treatment and aid kinesitherapy was born in the 1970s. Cryogenic temperatures can be applied topically or systemically, using a cryochamber.

The introduction of cryotherapy in therapeutic practice is attributed to the Japanese prof. Toshiro Yamauchi and

his team from the Reiken Rheumatism Village Institute in Oita, where the first portable cryotherapy devices were constructed and, in 1978, the first cryogenic chamber was developed. Another chamber was developed at the St Joseph's Rheumatology Clinic in Sendenhorst (Germany). In 1983, a cryotherapy applicator was developed for use in volunteers with rheumatism and post-traumatic diseases in the Department of Physiotherapy at the University of Physical Education in Wrocław, headed by Prof. Zdzisław Zagrobelny. In 1989, the first cryochamber was built in Poland (the second in Europe and the third in the world). A group of students from the Academy of Physical Education in Wrocław volunteered to test the device [2, 3].

New directions of research on the use of whole-body cryotherapy

The safety of WBC has been proven in clinical trials for people of all ages, provided that they are correctly qualified and that certain principles are followed. No life-threatening symptoms have been reported so far. The benefit-risk ratio is clearly favourable, with the treatments shown to improve the patient's general condition and clearly facilitating further rehabilitation. Any adverse effects, e.g. frostbites or raised blood pressure, should be immediately managed [2–4].

There is extensive literature on cryotherapy, local cryotherapy in particular. General indications include rheumatological diseases, osteoarthritis (RA), injuries and their complications, oedema, and local pain. In rheumatoid arthritis (RA), WBC significantly reduces pain and disease activity, allowing for lower analgesic use. These effects are likely due to changes in cytokine levels [5]. However, more research is needed on the effects of WBC on the human body.

The natural strengthening of the body through exposure to cold has become a tradition in many parts of the world. It is a method used to prevent diseases and promote healing that has evolved from pure empiricism in places where the climate promotes body hardening. It has been observed that exposure to cold blocks pain receptors by reducing afferent spindle discharges and transiently weakening nerve conduction. Furthermore, exposure to low temperatures suppresses pain perception, as a result of reduced muscle tone, cooling of muscles and nerves, deactivation of skin receptors and slowing of sensory and vegetative neuromuscular conduction, as well as it affects the rate of chemical reactions. This results in reduced pain perception, supported by the release of higher levels of β -endorphins and an effect on 'pain control gates' at the level of spinal cord and brainstem [5].

Cryotherapy, as a type of physical therapy, aims to eliminate or reduce pain, maintain optimal musculoskeletal function and arrest or at least slow the progression of degenerative changes. The therapeutic effects of WBC used in medicine are mainly related to reducing inflammatory processes and skeletal muscle tone, relieving pain and oedema, increasing muscle strength and accelerating regenerative and reparative processes. Systemic exposure to extremely low temperatures also leads to an increase in exercise tolerance and immunity, and has a beneficial

effects on the mental state, reducing hyperactivity, anxiety and restlessness, as well as improving perception, concentration, CNS fatigue resistance and sleep quality. Many studies have shown that kinesitherapy should be an integral part of cold treatment protocols [6].

WBC may be effective in the augmentation of antidepressants (reduced antidepressant intake was noted). The rapid antidepressant effect results from the release of endorphins immediately after treatment. Although the outcomes of WBC combined with antidepressant therapy obtained so far are interesting, they need to be replicated in further studies. Once the high efficacy of WBC and its rapid therapeutic effect are confirmed, this therapy may become an attractive option of augmenting antidepressant treatment, possibly also in drug-resistant depression [7].

Research has shown that systematic exposure to extreme cold air reduces IL-1 α , increases IL-6 and IL-10 cytokines, and contributes to a reduction in total antioxidant status (TAS) (a measure of antioxidant capacity of biological substances, such as lipid proteins, which is used in research on oxidative stress and oxidant effects) and has an overall immunostimulatory effect [8, 9]. To date, WBC has been proven to be effective in the treatment of somatic diseases such as RA, multiple sclerosis (MS), fibromyalgia, chronic back pain and ankylosing spondylitis [10, 11]. It was shown in one study that cryotherapy reduced depressive symptoms in patients with mild cognitive impairment, as measured by a visual analogue

scale (10 sessions, study group $n = 33$, temperature from -110°C to -160°C), justifying an attempt to use WBC in the treatment of depression [12].

Few publications have reported the use of WBC to support pharmacotherapy in depressive patients. They indicate that this method can lead to improvement in individuals already receiving pharmacological treatment. The severity of depressive symptoms decreased by about 35% during this time in the study with 10 WBC sessions, and by up to 69% in another study with 15 sessions. This may indicate a rapid and possibly dose-dependent effect of the treatment. There was no significant effect of 20 WBC sessions on changes in blood cell count, rheology and biochemistry in women with MS. WBC significantly increases erythrocyte capacity and lowers haematocrit (within physiological norms) in healthy women, which has a beneficial effect on the rheological properties of the blood. Whole body cryotherapy is a safe method in MS patients as changes in blood rheology are not responsible for therapeutic efficacy and WBC does not adversely affect the deformability and aggregation of red blood cells [13].

Studies on the use of WBC in obesity and post-coronavirus disease 2019 (COVID-19) condition (PCC) have also shown promising results. They have demonstrated that WBC is a safe therapy leading to overall improvement. They also showed that multidisciplinary rehabilitation is effective in post-COVID-19 patients and suggested that WBC is safe and may aid rehabilitation programmes [14].



Fig. 1. Whole-body cryochamber



Fig. 2. Patients before treatment session

General construction and operation of the most common Wrocław-type cryochamber

- WBC is performed using a special kit including:
 - an assembly of devices producing a gas cloud of defined size and temperature;
 - treatment chamber;
 - control panel.

The gas cloud generating unit works by transferring vapour-free compressed air to a heat exchanger into which liquid nitrogen, used here as a source of cold, is fed from a special tank in a controlled manner via an adjusting valve. In the heat exchanger, the liquid nitrogen reduces the temperature of the compressed air stream, which is fed through insulated tubes to the set of nozzles located in the treatment chamber. Unlike those used previously, modern WBC chambers allow patients to be observed through the glass and on a monitor, as well as to be spoken to via an inbuilt system, enabling direct contact. It is also possible to control the size of the gas cloud and, most importantly, to exclude the patient's head from the low-temperature exposure zone. The incoming cold air is systematically fed to the outside by a vacuum-based system. In this way it is possible to maintain a stable size of the cold gas cloud and to eliminate its effect on the temperature of the room where the treatment chamber is located.

The regulation and control devices in the control panel allow for setting the main treatment parameters, such as

temperature (from -120°C to -180°C) and pressure of both the compressed air and the expanding liquid nitrogen. Individual treatment parameters are set on an electronic board with a set of sensors. The treatment time, when the patient stands in the cold gas cloud, ranges from 1 to 4 minutes (usually 3 minutes). First, 3–4 patients enter the atrium (about -100°C) for 30 seconds each. The patients walk in circles throughout the treatment.

Qualification for a cycle of 10–20 sessions is performed by a doctor, after considering indications and contraindications for WBC. Blood pressure must be measured before entering the chamber. Participants should remove any metal jewellery and dry their skin if necessary. Patients wear special personal protective clothing that consists of socks, gloves, headband and face mask, as the air heated in the airways doubles its volume and deep exhalations may lead to respiratory distress [1–3].

Therapeutic properties of WCB

The effects of cryotherapy on the human body include:

- reduction of pain – increased release of β -endorphins and functional deactivation of sensory receptors and their connections to proprioceptors, slowed conduction in sensory fibres and functional deactivation of pain by 'control gates' according to Melzack and Wall's gate control theory of pain [1];
- reduction of oedema – several-hour active congestion in the tissues exposed to cryotherapy improves



Fig. 3. Patients after treatment session

metabolism and helps eliminate its products; improved blood flow as a result of cryotherapy combined with kinesitherapy has an oedema-reducing effect [1-3];

- relaxation of skeletal muscles and improvement of their strength – reduction of stimulus input to the medulla and segmental inhibition of gamma motor neuron stimulation and slowing down of conduction in motor neurons; analyses of EMG recordings after exposure to low temperatures and clinical observations confirmed that WBC significantly increases muscle strength [1-3];
- increased range of motion in the treated joints [1-3];
- increased serum adrenaline, noradrenaline, adrenocorticotrophic hormone, cortisol, and testosterone (in men). No increases in prolactin, follicle-stimulating hormone or 6-keto-PGF1 alpha have been reported [3];
- an increase in haemoglobin, leukocyte and platelet levels, as well as blood glucose and creatinine in blood cell count and biochemistry after 2 weeks compared to baseline; these values never exceeded the upper limit of normal [3].

The above data demonstrate an anti-inflammatory effect. The therapeutic effects persist for 2-4 hours, which are used for intensive kinesitherapy. Combining cryotherapy with kinesitherapy produces better outcomes [1-3].

The beneficial properties of WBC include:

- antioedematous, analgesic, anti-inflammatory effect, stimulating the body's natural regeneration processes;
- positive effect on well-being (helps relax);
- improving muscular, cardiovascular and lymphatic systems;
- improving the body's endurance by its hardening;
- regulation of blood flow and blood pressure as well as the cardiovascular system;
- rejuvenating effect on skin cells and stimulating other systems;
- reducing muscle spasticity while increasing muscle strength and flexibility;
- reducing stress symptoms.

Indications for use

Owing to its multiple properties, the cryochamber can be used to treat a wide range of diseases.

Indications for WBC [1-3]:

- treatment of rheumatic and degenerative diseases of the peripheral joints and spine;
- recovery from overload, post-traumatic muscle and joint disorders, discopathy and degenerative diseases;
- treatment of depressive syndromes and neuroses;
- physical rejuvenation for both amateur and professional athletes;
- auxiliary treatment of obesity and cellulite.

The following conditions are not contraindications to cryotherapy [1–3]:

- initial stage of systemic lupus erythematosus;
- early stage of systemic scleroderma;
- diabetes mellitus;
- varicose veins of the lower extremities;
- paroxysmal tachycardia;
- metal in deeper tissues;
- Raynaud's phenomenon;
- malignancies – local cryotherapy may be used in patients with no contraindications as confirmed by an oncologist.

Contraindications

Absolute contraindications to WBC [1–3]:

- severe heart disease and heart failure, post-MI syndrome, stage 3 hypertension, advanced atherosclerosis, thromboembolic and inflammatory venous changes;
- lung diseases – with the exception of asthma (cold reduces bronchial muscle tone);
- cold intolerance;
- paroxysmal haemoglobinuria;
- frostbites, cachexia, debilitation;
- active hyperthyroidism and hypothyroidism;
- skin sensory disturbances, open wounds and ulcers;
- febrile conditions;
- acute infections;
- kidney disease;
- claustrophobia, epilepsy, mental illness and excessive sweating;
- use of certain medications and stimulants such as antipsychotics, alcohol;
- advanced atherosclerosis.

Relative contraindications to WBC [1–3]:

- age > 65 years;
- heart valve defects;
- exertional and spontaneous angina pectoris;
- cardiac arrhythmias >100/min;
- history of venous thrombosis and peripheral arterial embolism;
- emotional lability, which may be expressed, among other things, by increased sweating of the skin.

Discussions on the effectiveness of cold therapy

Given that there are only 30,000 heat receptors and up to 250,000 cold receptors in the human body, and that the adaptation time to low temperature is many-fold shorter compared to high temperature, it could be expected that cold treatment should be more effective than heat treatment. In fact, this has been confirmed by research; however, there is no consensus at what temperature cryotherapy starts. For example, heat loss at the same temperature is approximately 250 times greater in water than in air. For this reason, immersion in icy water (winter swimming) has a greater effect on the body than a stay in a cryochamber, although a comparison of temperatures of 0°C and –180°C may lead to a dif-

ferent conclusion. Also for this reason, ice-water baths are much more challenging than cryochamber treatments and are therefore theoretically recommended mainly for healthy individuals, including athletes. Thus, it is not the temperature that determines the strength of a given treatment, but the intensity of the stimulus adequately selected for the purpose of treatment [15–17]. Winter swimming, which is a popular leisure activity, appears to be less safe than WBC. More research is clearly needed. However, there is a lot of research on the beneficial effects of cold exposure to reduce pain [18]. The authors of a four-week study on the effects of WBC and static stretching (SS) came to some interesting conclusions. The aforementioned studies showed that WBC reduces the severity of some symptoms of chronic fatigue syndrome. This is observed immediately after therapy. The authors of the four-week study on WBC and SS assessed the effects of these treatments on the autonomic nervous system and fatigue levels. They suggested the need to assess treatment outcomes, the duration of improvement and symptoms after a four-week follow-up. In this study, peripheral and aortic systolic blood pressure decreased one month after WBC combined with SS compared to before. The effects of WBC and SS on the reduction of fatigue, aortic stiffness indices and the severity of symptoms of autonomic nervous system disorders and improvement in cognitive function persisted for one month. However, improvements in all three fatigue measurement tools (Chalder Fatigue Questionnaire, Fatigue Impact Scale and Fatigue Severity Scale) were reported for 17 out of 22 patients [19].

Conclusions

The discussed form of modern therapy, stemming from the traditional use of cold in the treatment of pain, seems to offer hope to our society, which is increasingly affected by lifestyle changes (poor diet, lack of exercise) occurring at an increasingly earlier age, leading to early disability, joint pain, muscle atrophy and contractures that may contribute to greater susceptibility to injuries. Disorders such as obesity and depression are also becoming more common. In both cases, the cause can be traced to lifestyle changes.

Inadequate diet and poor physical activity from an early age give rise to so-called 'lifestyle diseases' at an increasingly early age. WBC appears to be an ideal therapeutic option for such patients as cold reduces pain that can occur even in fibromyalgia [19]. Among other things, it is an optimal approach for chronic pain in patients with osteoarthritis, RA and other rheumatic diseases, as well as MS. WBC can reduce the need for high doses of NSAIDs and opioids, as confirmed by recent studies. The use of WBC, which reduces pain, exhibits anti-oedematous and anti-inflammatory effects, could become a solution to many lifestyle diseases. Obesity and depression are also the consequences of a poor lifestyle [20]. Here, research into the use of WBC also seems to confirm the effectiveness of this form of treatment and offers some hope for the developing society.

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THE IMPACT OF TIRZEPATIDE ON LIPID PROFILE BASED ON THE SURMOUNT CLINICAL TRIALS

Analiza wpływu tirzepatydru na profil lipidowy
na podstawie badań klinicznych SURMOUNT



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Abstract

Hyperlipidaemia, or high blood lipid levels, is a significant risk factor for cardiovascular diseases. Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide receptor and the glucagon-like peptide-1 receptor. Tirzepatide is indicated for patients with type 2 diabetes and adults with obesity and overweight to reduce body weight. In recent years, there have been reports that this drug also has beneficial effects on the lipid profile. This paper summarizes data from the SURMOUNT clinical trials to evaluate how tirzepatide affects lipid profile parameters. The analysis demonstrated numerous benefits resulting from tirzepatide therapy. The observed favourable safety profile additionally enhances the attractiveness of this drug as a therapy for individuals with lipid disorders. Tirzepatide could be a breakthrough drug not only for obesity and type 2 diabetes but also for dyslipidaemia. However, despite promising results, further research is needed to understand the long-term safety and cost implications associated with this agent. These studies will be crucial for developing individualized therapeutic plans and optimizing the use of tirzepatide in various patient subgroups.

Streszczenie

Hiperlipidemia, czyli wysokie stężenie lipidów we krwi, stanowi istotny czynnik ryzyka chorób sercowo-naczyniowych. Tirzepatyd to podwójny agonista receptorów polipeptydu insulinotropowego zależnego od glukozy oraz glukagonopodobnego peptydu-1. Według wskazań lek ten stosuje się w cukrzycy typu 2 oraz otyłości i nadwadze u dorosłych pacjentów w celu redukcji masy ciała. W ostatnich latach pojawiły się także doniesienia, że tirzepatyd korzystnie wpływa na profil lipidowy. W pracy podsumowano dane z badań klinicznych SURMOUNT, aby ocenić, jak tirzepatyd wpływa na profil lipidowy. Analiza wykazała wiele korzyści wynikających z przyjmowania tego leku. Dodatkowo korzystny profil bezpieczeństwa podnosi jego atrakcyjność jako leku stosowanego u osób z zaburzeniami lipidowymi. Tirzepatyd może być przełomowym lekiem w leczeniu nie tylko otyłości i cukrzycy typu 2, ale także dyslipidemii. Jednak pomimo obiecujących wyników, potrzebne są dalsze badania, aby zrozumieć długoterminowe bezpieczeństwo i koszty związanych ze stosowaniem tego leku. Będą one kluczowe dla opracowania indywidualnych planów terapeutycznych i optymalizacji wykorzystania tirzepatyd w różnych podgrupach pacjentów.

Keywords: lipid profile; tirzepatide; SURMOUNT

Słowa kluczowe: profil lipidowy; tirzepatyd; SURMOUNT

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Introduction

Lipid disorders are a major risk factor for cardiovascular disease (CVD) both in Poland and worldwide. They affect up to 21 million people, accounting for more than 60% of the adult population and up to 70% of >65 year-old population, in Poland. It is estimated that only 20% of the population are aware of their total or LDL cholesterol levels. Unawareness of lipid disorders prevents treatment initiation, leading to an increased risk of serious cardiovascular incidents, such as myocardial infarction and stroke [1].

High LDL cholesterol plays an important role in the pathogenesis of atherosclerosis. However, in the last two decades, many studies have demonstrated that excess cholesterol accumulation in various tissues and organs also contributes to the development of many other disorders. A positive correlation was found between hyperlipidaemia and chronic kidney disease, osteoporosis, Alzheimer's disease, non-alcoholic fatty liver disease, hypothyroidism and pituitary disorders [2].

Since hyperlipidaemia is a well-known modifiable risk factor for cardiovascular disease (CVD), its treatment is of particular importance. The primary treatment for hyperlipidaemia involves lifestyle management, including increased physical activity and an appropriate diet. Those with poor response to lifestyle changes are offered pharmacotherapy. Various lipid-lowering therapies are currently available, including statins, ezetimibe, PCSK9 inhibitors and ion-exchange resins [3]. There is also ample ongoing research on new blood lipid lowering treatments [4, 5]. Tirzepatide (TZP) is one of the possible future therapeutic options. To date, a number of randomised controlled trials have been conducted in different countries to assess the efficacy and safety of this drug. However, most of these mainly focused on assessing its impact on blood glucose and body weight in patients with or without type 2 diabetes mellitus (T2DM). Only a small number of studies have analysed the effect of this agent on lipid metabolism.

Aim

The aim of this paper was to summarise and analyse the current knowledge on the impact of TZP on the lipid profile based on the SURMOUNT trials.

Mechanism of action

Tirzepatide is a dual agonist of gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Its mechanism of action is to mimic incretin hormones by interacting with GLP-1 and GIP receptors. GLP-1 is released by intestinal cells in response to ingested food to regulate blood glucose. Tirzepatide acts in a glucose-dependent manner, increasing insulin secretion by pancreatic β -cells in response to elevated blood glucose. It also inhibits the release of glucagon and delays gastric emptying. GLP-1 receptors are not only found in the pancreas, but also in various other organs and systems, such as the central nervous system, heart, kidneys, lungs and gastrointestinal tract. There is evidence to suggest that

GLP-1 may not only regulate glucose levels and suppress appetite, but also has neurotrophic, neuroprotective and cardioprotective effects [6].

The action of TZP on the GIP receptor generates an effect similar to its agonist action on the GLP-1 receptor, stimulating insulin release from pancreatic β -cells. However, unlike its action on GLP-1 receptors, activation of the GIP receptor does not affect glucagon levels and has minimal impact on gastric digestive processes. The synergistic effect on both receptors is beneficial and effectively stabilises blood glucose levels [7].

Tirzepatide increases satiety and reduces hunger, suppressing appetite. As a result, the patient shows a reduced desire to eat, which in turn reduces body weight and body fat. This phenomenon has a beneficial effect on the patient's lipid profile. The exact mechanism of action of incretin hormone agonists on adipocytes is not fully understood. They are likely to act mainly indirectly by increasing sympathetic nervous system stimulation, leading to reduced lipogenesis and lower blood triglycerides [8].

The history of tirzepatide

Tirzepatide was invented by Eli Lilly and Company. In 2016, a phase I trial was launched with the main objectives of:

- assessing TZP safety and its possible adverse events;
- measuring TZP pharmacokinetics, i.e. distribution and elimination time;
- assessing the effects of TZP on blood glucose levels [9].

A year later, phase II trial was initiated to evaluate the efficacy of the investigational medicinal product in T2DM patients [10]. The results of the SURPASS clinical trial were published between 2020 and 2022. The phase III SURPASS programme was designed to assess the efficacy and safety of TZP as a therapy to improve blood glucose control in T2DM patients. The SURPASS programme comprises six global (SURPASS 1-6) [11-16], two Japanese (SURPASS-J mono, SURPASS-J combo) and one Asian-Pacific study (SURPASS-AP combo) [17-19]. The SURPASS study resulted in a decision by the US Food and Drug Administration (FDA) in May 2022 to approve TZP under the trade name Mounjaro. Treatment of T2DM in adults alongside appropriate diet and physical activity was the main indication. On 6 October 2022, the FDA granted Fast Track designation for TZP in the context of trials on the treatment of adults with obesity, or overweight with weight-related comorbidities [20]. As a result, the SURMOUNT programme was conducted between 2022 and 2023. On its basis, the FDA approved TZP under the trade name Zepbound for chronic weight management in adults with obesity (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) with at least one weight-related condition (e.g. hypertension, dyslipidaemia, T2DM, obstructive sleep apnoea or CVD) in November 2023. Tirzepatide is intended to be used alongside a reduced-calorie diet and increased physical activity [21].

SURMOUNT trials – background

The SURMOUNT project is an innovative research endeavour to evaluate the efficacy and safety of TZP as a therapy for overweight and obese individuals. Under this programme, multicentre, randomised and double-blind clinical trials ensuring a high level of reliability of the results were conducted. The SURMOUNT programme encompasses five phase III clinical trials. SURMOUNT-1 (NCT04184622) and SURMOUNT-2 (NCT04657003) assessed the efficacy and safety of TZP used at different doses. SURMOUNT-1 evaluated only patients without T2DM, while SURMOUNT-2 included only T2DM patients [22, 23]. SURMOUNT-3 (NCT04657016) and SURMOUNT-4 (NCT04660643) were designed to assess the efficacy and safety of TZP at maximum tolerated doses [24, 25]. SURMOUNT-5 was designed to compare TZP with semaglutide for efficacy and safety in non-diabetic overweight or obese adults with weight-related health problems. This study is currently underway and is expected to be completed in November 2024 [26]. The inclusion criteria for SURMOUNT-1, SURMOUNT-3, SURMOUNT-4, and SURMOUNT-5 were almost identical, with some differences for the SURMOUNT-2 trial, especially in terms of BMI values. All participants followed a reduced-calorie diet and increased their physical activity when entering the study. All patients were of legal age and gave

informed consent to participate in the study. The trials were conducted in accordance with the recommendations for good clinical practice and the principles of the Declaration of Helsinki. Methodological details for each SURMOUNT study are summarised in table 1.

At baseline, demographic and clinical data were collected, including patients' sex and age, BMI, fasting body weight, waist circumference, as well as systolic and diastolic blood pressure. Metabolic parameters such as fasting glucose, HbA_{1c} and fasting lipids were also assessed. Body weight, HbA_{1c}, blood pressure and lipid profile were the primary endpoints of the study.

Table 2 summarises patients' demographic, anthropometric and clinical parameters, allowing analysis of their baseline health status.

A total of 5,066 patients participated in SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4. Women predominated in all studies, accounting for a total of 64.55% of patients. Total cholesterol ranged between 176.8 mg/dL and 194.6 mg/dL. The lowest (44.3 mg/dL) and the highest (51.1 mg/dL) HDL levels were observed in SURMOUNT-2 and SURMOUNT-4, respectively. LDL levels ranged from 96.5 mg/dL to 116.8 mg/dL, depending on the study, while VLDL ranged from 60.4 mg/dL to 77.7 mg/dL. The lowest (135.7 mg/dL) and the high-

Table 1. Study objectives, inclusion criteria and methodology of the SURMOUNT clinical trial programme

Title	SURMOUNT-1 [22]	SURMOUNT-2 [23]	SURMOUNT-3 [24]	SURMOUNT-4 [25]	SURMOUNT-5 [26]
Number	NCT04184622	NCT04657003	NCT04657016	NCT04660643	NCT05822830
Objectives	To assess the efficacy and safety of TZP in obese or overweight adults	To assess the efficacy and safety of TZP in adults with obesity and T2DM	To investigate how TZP maintains BW or contributes to further BW loss in obese individuals following lifestyle modification	To assess the efficacy and safety of TZP used alongside diet and physical activity in adults with obesity or overweight	To assess the efficacy and safety of TZP vs. sema in obese or overweight adults with weight-related comorbidities
Inclusion criteria	BMI ≥30 kg/m ² , ≥1 comorbidity*, ≥1 weight loss failure, age ≥18 years	BMI ≥27 kg/m ² , T2DM**, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m ² , ≥1 comorbidity*, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m ² , ≥1 comorbidity*, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m ² , ≥1 comorbidity*, ≥1 weight loss failure, age ≥18 years
Randomisation	+	+	+	+	+
Double-blinded	+	+	+	+	-
PBO	+	+	+	+	-
Intervention	Once-weekly TZP (5 mg, 10 mg, 15 mg) and PBO at 1:1:1	Once-weekly TZP (10 mg, 15 mg) and PBO at 1:1:1	Once-weekly TZP MTD (10 mg or 15 mg) and PBO at 1:1	Once-weekly MTD TZP (10 mg or 15 mg) and PBO at 1:1	Once-weekly TZP 15 mg and sema 2.4 mg
Duration	72 weeks	72 weeks	72 weeks	88 weeks	74 weeks

TZP – tirzepatide; T2DM – type 2 diabetes mellitus 2; BMI – body mass index; PBO – placebo; sema – semaglutide; BW – body weight; MTD – maximum tolerated dose

* Hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease

** The study included patients with T2DM with HbA_{1c} ≥7% to ≤10% at screening, with stable therapy for the last 3 months prior to the study

est (184.4 mg/dL) triglyceride levels were recorded in SURMOUNT-4 and SURMOUNT-2. Free acids were similar across all studies and ranged between 0.51 mEq/L and 0.6 mEq/L.

Analysis of results

The SURMOUNT trial programme demonstrated significantly improved lipid profile in TZP-treated patients compared to placebo as evidenced by percentage changes in laboratory parameters such as triglycerides, total cholesterol, LDL, VLDL, non-HDL, HDL, and free fatty acids compared to baseline. SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4 assessed statistical significance between the outcomes achieved by TZP-treated patients vs. placebo, while SURMOUNT-3 did not report *p*-values for changes in lipid profile parameters.

The greatest (33.3%) reduction in triglycerides was observed in SURMOUNT-4 patients, who were receiving the maximum tolerated dose (fig. 1). This was statistically significantly higher compared to placebo, which showed a 15.3% decrease (*p* <0.001). SURMOUNT-1 and SURMOUNT-2 also demonstrated a statistically significant difference (*p* <0.001) between the TZP-treated groups (decrease between 24.3–31.3%) and placebo. The reduction in total cholesterol in TZP-treated patients was 7.4–3% and was greater compared to placebo, where the changes ranged from –1.1% to +5.2%. SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4 showed statistically significant differences (*p* <0.05) between patients treated with TZP and those receiving placebo. The largest decrease in total cholesterol was observed in SURMOUNT-1, in the group receiving TZP 15 mg. Changes in LDL ranged from –8.6% to +2.3% in TZP-treated patients and from –0.9% to +6.3% in the placebo group (fig. 2). These differences were statistically significant (*p* <0.05) across SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4. The change in non-

HDL cholesterol levels ranged from –13.4% to –6.6% in the TZP-treated group and from –1.8% to +5.6% in the placebo group. These differences were statistically significant (*p* <0.05) across SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4. HDL increased in TZP-treated patients from 15.4% to 7%, with an increase of 9.4% to 0.2% compared to placebo. These differences were statistically significant in SURMOUNT-1 and SURMOUNT-2. In contrast, no statistical significance (*p* >0.05) was found in SURMOUNT-4 despite using the maximum tolerated dose of TZP, with 12.3% increase in HDL in the TZP-treated group vs. 9.4% in the placebo group (fig. 3). The change in VLDL ranged from –32.6% to –24.2% in TZP-treated patients and from –6% to +3% in the placebo group. The change in free fatty acids ranged from –33.1% to –0.7% in TZP-treated patients, and from –15% to +6.1% in the placebo group. There were significant differences in VLDL and free fatty acids with respect to baseline between the TZP-treated group and the placebo group in SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4.

Safety analysis

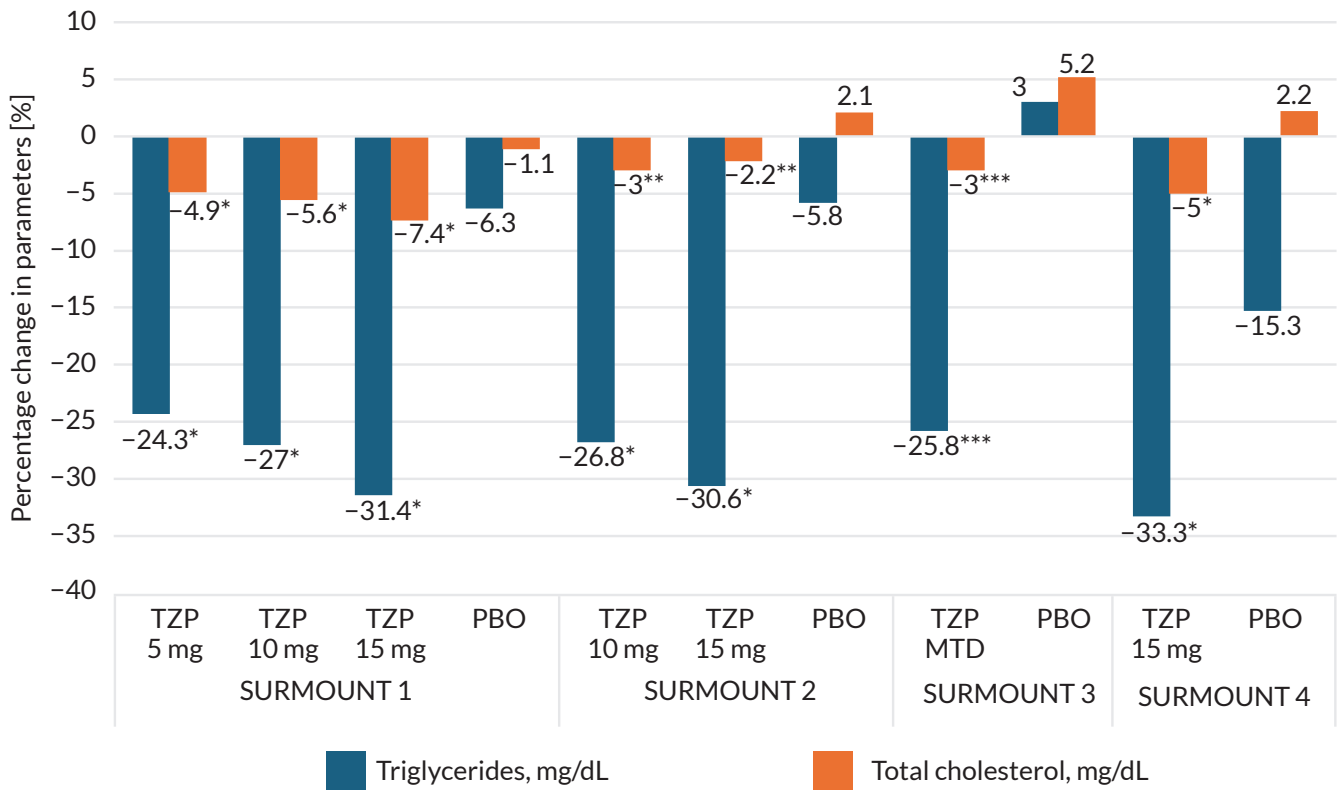
It was observed in SURMOUNT-1 that the proportion of patients reporting at least one treatment-emergent adverse event (TEAE) during TZP therapy ranged from 78.9% to 81.8% compared to 72% in the placebo group. Gastrointestinal symptoms such as nausea, diarrhoea and constipation were the most common TEAEs. A total of 160 cases of serious adverse events (SAE) were reported (6.3%). However, it should be emphasised that their incidence was similar between patients receiving TZP and placebo.

In SURMOUNT-2, 74.48% of TZP-treated patients reported at least one TEAE and a similar rate was reported for placebo (75.87%). Adverse events led to study withdrawal in 35 TZP-treated patients and 12 patients in the placebo group.

Table 2. Baseline characteristics of patients included in SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, SURMOUNT-4

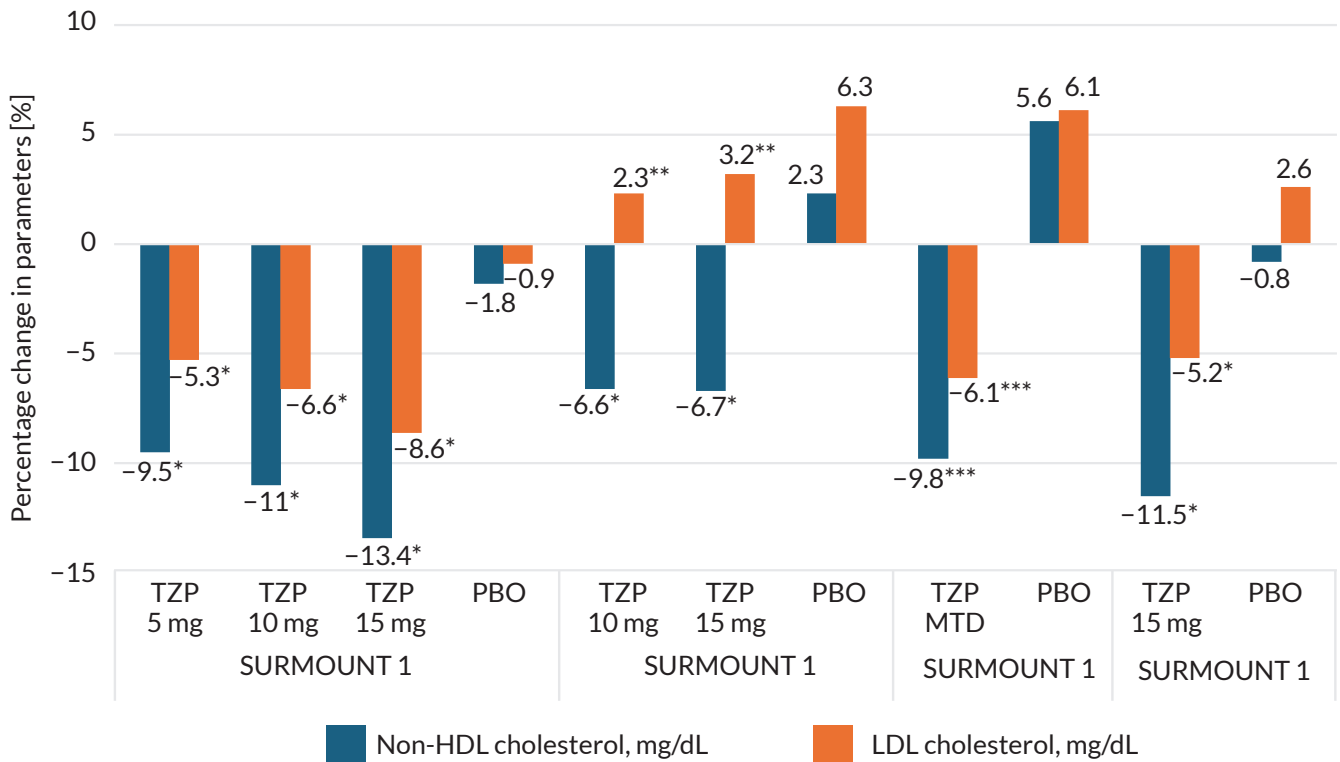
Title	SURMOUNT-1 [22]	SURMOUNT-2 [23]	SURMOUNT-3 [24]	SURMOUNT-4 [25]
Number	NCT04184622	NCT04657003	NCT04657016	NCT04660643
Number of patients (n)	2,539	938	806	783
Women, n (%)	1,714 (67.5)	476 (50.7)	534 (66.3)	546 (69.7)
Age (years), ± SD	44.9 ± 12.5	54.2 ± 10.6	44.9 ± 12.5	47.6 ± 12.9
Body weight (kg), ± SD	104.8 ± 22.1	100.7 ± 21.1	109.7 ± 24.2	107.0 ± 22.5
BMI (kg/m ²) ± SD	38.0 ± 6.8	36.1 ± 6.6	38.9 ± 7.1	38.3 ± 6.6
Total cholesterol (mg/dL) ± SD	191.7 ± 38.8	176.8 ± 42.0	194.6 ± 37.4	191.9 ± 39.2
HDL (mg/dL) ± SD	48.9 ± 13.0	44.3 ± 11.5	50.3 ± 13.9	51.1 ± 13.1
LDL (mg/dL) ± SD	114.2 ± 32.7	96.5 ± 34.7	116.8 ± 31.1	113.8 ± 32.9
VLDL (mg/dL) ± SD	63.9 ± 29.6	77.7 ± 33.6	60.8 ± 28.4	60.4 ± 27.9
Triglycerides (mg/dL) ± SD	145.7 ± 105.1	184.4 ± 127.9	138.2 ± 87.9	135.7 ± 78.6
Free fatty acids (mEq/L) ± SD	0.51 ± 0.21	0.60 ± 0.23	0.55 ± 0.22	0.53 ± 0.22

HDL – high-density lipoprotein; LDL – low-density lipoprotein; VLDL – very low-density lipoprotein; BMI – body mass index; SD – standard deviation



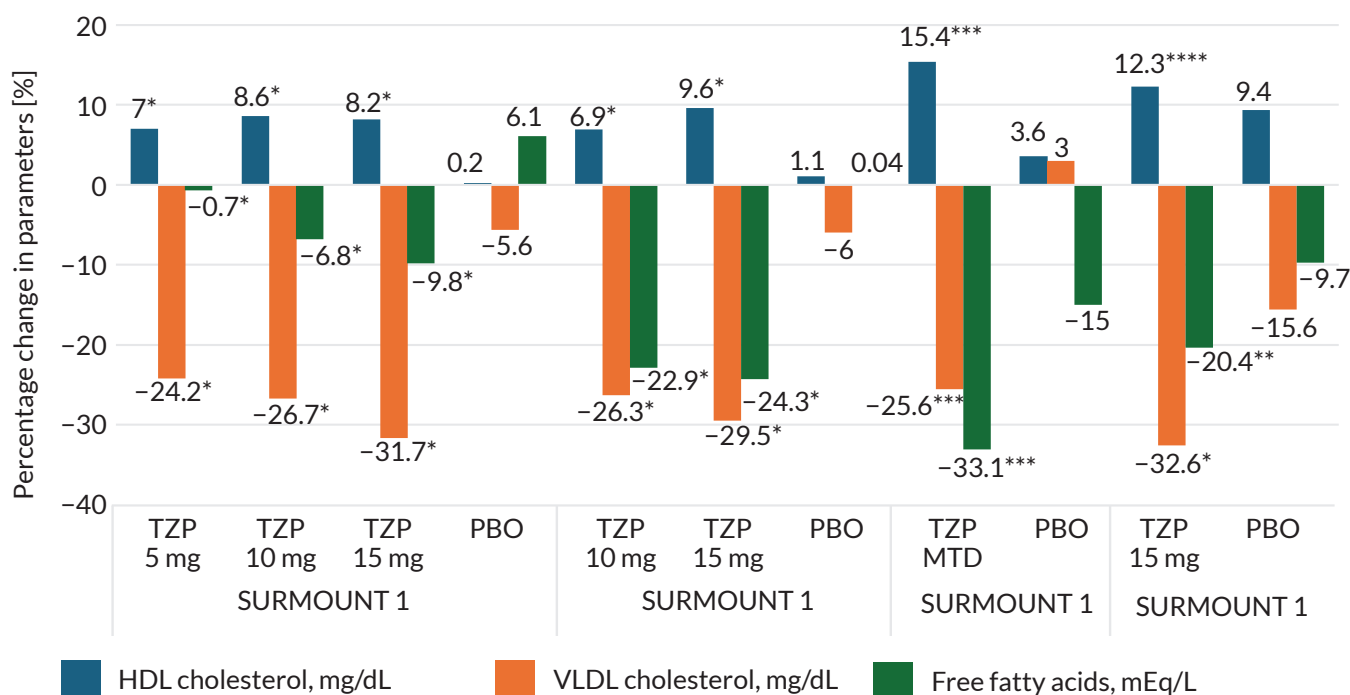
TZIP - tirzepatide; PBO - placebo; MTD - maximum tolerated dose
 The p-value refers to the comparison between the drug at a given dose and placebo.
 * p < 0.001, ** p = 0.001-0.05, *** Not reported

Figure 1. Comparison of percentage changes in triglycerides and total cholesterol in across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4



TZIP - tirzepatide; PBO - placebo; MTD - maximum tolerated dose
 The p-value refers to the comparison between the drug at a given dose and placebo.
 * p < 0.001, ** p = 0.001-0.05, *** Not reported

Figure 2. Comparison of percentage changes in non-HDL and LDL across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4



TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose
The p-value refers to the comparison between the drug at a given dose and placebo.
* $p < 0.001$, ** $p = 0.001-0.05$, *** Not reported, **** $p > 0.05$

Figure 3. Comparison of percentage changes in HDL, VLDL and free fatty acids across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4

In SURMOUNT-3, the overall proportion of patients who reported at least one TEAE was 87.1% in the TZP group (287 patients), and 76.7% in the placebo group (292 patients). Gastrointestinal symptoms such as nausea, diarrhoea and constipation were the most common TEAEs. These were more common in patients receiving the maximum tolerated dose of TZP than in the other groups.

In SURMOUNT-4, 81.0% of participants reported at least one TEAE during TZP therapy. Gastrointestinal TEAEs such as nausea (35.5%), diarrhoea (21.1%),

constipation (20.7%) and vomiting (16.3%) were most common. These symptoms were more frequent in the TZP group vs. placebo.

A detailed analysis of TZP safety profile in the SURMOUNT study is shown in table 3.

Conclusions

Despite the well-known pathological consequences of hyperlipidaemia, there is little public awareness of the

Table 3. SURMOUNT – safety analysis

Study	Investigated subgroup	Patients with ≥ 1 AE, n (%)	Serious TEAEs, n (%)	TEAEs leading to treatment discontinuation, n (%)
SURMOUNT-1 [22]	TZP 5 mg (n = 630)	510 (80.95)	40 (6.35)	27 (4.29)
	TZP 10 mg (n = 636)	520 (81.76)	44 (6.92)	45 (7.08)
	TZP 15 mg (n = 630)	497 (78.89)	32 (5.01)	39 (6.19)
	PBO (n = 643)	463 (72.01)	44 (6.84)	17 (2.64)
SURMOUNT-2 [23]	TZP 10 mg (n = 312)	242 (77.56)	18 (5.77)	12 (3.85)
	TZP 15 mg (n = 311)	222 (71.38)	27 (8.68)	23 (7.40)
	PBO (n = 315)	239 (75.87)	23 (7.30)	12 (3.81)
SURMOUNT-3 [24]	TZP MTD (n = 287)	250 (87.12)	17 (5.92)	30 (10.45)
	PBO (n = 292)	224 (76.71)	14 (4.79)	6 (2.05)
SURMOUNT-4 [25]	TZP MTD (n = 335)	202 (60.30)	10 (2.99)	6 (1.79)
	PBO (n = 335)	187 (55.82)	10 (2.30)	3 (0.89)

TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose; TEAE – treatment-emergent adverse event

benefits of treating this disorder. The new treatment, tirzepatide, seems a promising alternative for the management of hyperlipidaemia. This review summarised the efficacy and safety of TZP based on the results of the phase III SURMOUNT clinical trials. These trials have shown that TZP not only effectively regulates blood glucose and leads to weight loss in T2DM patients, but it also significantly reduces blood lipids, with a relatively favourable safety profile. These studies are a key step in assessing the efficacy of this drug and its potential introduction into clinical practice. Continued research assessing the effects of TZP on the lipid profile and metabolic syndrome is needed. Despite such promising results, attention should be paid to gastrointestinal adverse events. Although these were mostly mild to moderate, further research is needed to better understand the long-term consequences of TZP therapy and to reduce the risk of treatment-emergent adverse events.

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ORAL HYGIENE IN 6–13-YEAR-OLDS UNDERGOING ORTHODONTIC THERAPY: THE IMPACT OF PARENTAL INVOLVEMENT ON ORAL HEALTH OUTCOMES



Higiena jamy ustnej u dzieci w wieku 6–13 lat poddawanych terapii ortodontycznej: wpływ zaangażowania rodziców lub opiekunów na wyniki w zakresie zdrowia jamy ustnej

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Abstract

Introduction: Oral hygiene is a crucial element during orthodontic treatment, particularly when patients use removable orthodontic appliances. In the 9–13 year age group, when oral cavity development is still dynamic, proper hygiene can affect the effectiveness of orthodontic therapy and prevent complications, such as tooth decay or gingivitis. Additionally, parental involvement can significantly impact the oral hygiene routine of children in this age group. **Aim:** The objective of this study was to assess the oral hygiene status in 9–13-year-olds using removable orthodontic appliances under care covered by the National Health Fund. Additionally, the study aimed to investigate the influence of parental involvement on the oral hygiene of these patients. **Methods:** Patients aged 9–13 years undergoing treatment with removable orthodontic appliances under the National Health Fund were included in the study. The oral hygiene status of patients was assessed using standard tools, such as the Oral Hygiene Index (OHI-S) and decay indices. Parents or guardians of patients were asked to complete a survey on the oral hygiene routine of their children and their involvement in maintaining their children's oral hygiene during orthodontic treatment. Data were subjected to statistical analysis to assess the relationship between oral hygiene status and parental/guardian influence. **Conclusions:** The anticipated conclusions from the study may help identify factors influencing effective oral hygiene in children using removable orthodontic appliances. Knowledge about the role of parents or guardians in oral hygiene care could lead to the development of educational strategies aimed at improving oral hygiene status in this patient group.

Streszczenie

Wstęp: Higiena jamy ustnej jest istotnym elementem podczas leczenia ortodontycznego, zwłaszcza gdy pacjenci korzystają z ruchomych aparatów ortodontycznych. W grupie wiekowej 9–13 lat, kiedy rozwój jamy ustnej jest jeszcze dynamiczny, właściwa higiena może wpłynąć na skuteczność leczenia ortodontycznego i zapobiec powikłaniom takim jak próchnica czy zapalenie dziąseł. Zaangażowanie rodziców lub opiekunów może znacząco wpłynąć na higienę jamy ustnej dzieci w tej grupie wiekowej. **Cel badania:** Celem pracy jest ocena stanu higieny jamy ustnej pacjentów w wieku 9–13 lat korzystających z ruchomych aparatów ortodontycznych, objętych opieką finansowaną ze środków Narodowego Funduszu Zdrowia. Dodatkowo celem badania było zbadanie wpływu rodziców lub opiekunów na higienę jamy ustnej tych pacjentów. **Metody:** Do badania zostali wybrani pacjenci w wieku 9–13 lat, leczeni aparatami ortodontycznymi ruchomymi w ramach Narodowego Funduszu Zdrowia. Stan higieny jamy ustnej pacjentów oceniano przy użyciu standardowych wskaźników, takich jak wskaźnik higieny jamy ustnej (OHI-S) i wskaźniki próchnicy. Rodzice lub opiekunowie pacjentów zostali poproszeni o wypełnienie ankiety dotyczącej higieny jamy ustnej ich dzieci oraz ich zaangażowania w utrzymanie higieny jamy ustnej podczas leczenia ortodontycznego. Dane poddano analizie statystycznej w celu oceny związku pomiędzy wpływem rodziców lub opiekunów a stanem higieny jamy ustnej. **Wnioski:** Wnioski z badania mogą pomóc w identyfikacji czynników wpływających na skuteczną higienę jamy ustnej u dzieci stosujących ruchome aparaty ortodontyczne. Wiedza na temat roli rodziców lub opiekunów w dbaniu o higienę jamy ustnej mogłaby pozwolić na opracowanie strategii edukacyjnych mających na celu poprawę stanu higieny jamy ustnej w tej grupie pacjentów.

Keywords: hygiene; removable appliances; orthodontics; the role of parents in treatment

Słowa kluczowe: higiena; aparaty ruchome; ortodoncja; rola rodziców w leczeniu

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Introduction

The aim of orthodontic treatment is to improve oral health. In early school children, it mainly uses removable orthodontic appliances. Treatment for children at this age is offered as part of reimbursable care until the age of 13 years. Parents are referred with children to orthodontic clinics by dentists and speech therapists, but also a result of their own concerns about their children's oral health.

Orthodontic treatment is associated with the risk of various complications [1–3]. Failure to comply with medical recommendations to maintain hygiene regime often leads to complications during removable orthodontic appliance therapy. Neglect of oral hygiene typically leads to microecological imbalance. Plaque accumulates on both tooth surfaces and removable braces. It is an aetiological factor for inflammation in the oral cavity. As a result, patients undergoing orthodontic treatment are more likely to develop gingivitis. They are also found to have an increased risk of dental caries [4, 5].

Therefore, the patient's oral hygiene should be assessed on the first orthodontic visit and, if necessary, oral hygiene instructions should be provided. In cases of very poor hygiene, orthodontic treatment should be postponed until it has improved to at least a satisfactory level [6]. Children receiving orthodontic appliances should be instructed on their use. Patients and their parents are also provided with precise information on how to clean the device [7–9].

When working with children, all instructions should be mostly directed to their parents [8].

Oral hygiene education involving children and their parents significantly improves treatment efficacy, as well as translates into improved oral health and optimal orthodontic outcomes [8–10].

Aim

The aim of this study was to assess the oral hygiene status of children receiving orthodontic treatment with removable appliances at an orthodontic clinic. Children's oral hygiene was checked during three consecutive visits to investigate the impact of an educational programme for children and their parents on improving hygiene practices. Additionally, the study aimed to assess parental

role in shaping the quality of oral hygiene procedures performed by children.

Materials and methods

The parents of children undergoing orthodontic treatment were asked to complete an author's questionnaire to investigate the extent to which children were instructed, accompanied and supervised during hygiene procedures. The questionnaire enquired about the duration and manner in which the children brushed their teeth, and the toothpaste used.

The survey also assessed parental knowledge about oral hygiene:

- Do the parents know the correct technique for tooth brushing and use additional hygiene methods, such as mouthwash and flossing?
- Do parents know how long and how often teeth should be brushed?
- How do parents themselves implement oral hygiene and is it done properly?

The survey also included questions on the use of recommendations for cleaning the removable appliances (method and frequency).

At the visit prior to providing removable appliances, the children were checked for oral hygiene. If the level of hygiene was considered unsatisfactory, brushing instructions were given. The instructions were adapted to the child's developmental level. Parents were invited to participate in tooth brushing training in order to involve them in the process of learning, monitoring and reinforcing their child's hygiene. If the hygiene was considered satisfactory or appropriate, the child was given positive reinforcement and instructions to further maintain oral hygiene habits.

At this visit, the child's caregivers were instructed, depending on the child's needs and age, to assist with or supervise oral hygiene.

During another appointment, when the child was provided with orthodontic appliance, oral hygiene was reviewed. If necessary, patients and their parents were again educated on hygiene procedures. Parents and children were informed about the consequences of neglect in this area. Advice on oral hygiene was adjusted to the patients' age and their ability to understand. The

Table 1. Oral hygiene at visit 1

Patient age (years)/number of patients in a group	Hygiene level % (n)		
	Very good	Good	Moderate
6-7/ 10 patients	10% (1)	20% (2)	30% (3)
8-10/ 15 patients	13.3% (2)	13.3% (2)	20% (3)
11-13/ 30 patients	10% (3)	16.6% (5)	33.3% (10)

Table 2. Hygiene levels as declared by caregivers

Very good	Good	Moderate	Bad
10%	25%	55%	10%

importance of oral hygiene was also discussed with the patients' parents.

At the next follow-up visit, 2 months after providing patients with appliances, the oral hygiene status was checked in relation to previous visits and the hygiene status of the appliance was assessed.

The Oral Hygiene Index (OHI) was used for the assessment.

Due to the age of patients, dental plaque accumulation was assessed using the Simplified Oral Hygiene Index (OHI-S).

Evaluation criteria:

- 0 – no debris;
- 1 – soft debris covering up to 1/3 of the exposed tooth surface;
- 2 – soft debris covering up to 2/3 of the exposed tooth surface;
- 3 – debris covering up to 2/3 of the exposed tooth surface.

Each indicator should be assessed separately. OHI-S, which scores only 6 surfaces (teeth 11, 16, 26, 36, 31, 46), is most commonly used. The buccal surfaces of the upper molars, the lingual surfaces of the lower molars and the labial surfaces of incisors are typically assessed.

Result interpretation by category:

- 0–1.2 – good hygiene;
- 1.3–3.0 – moderate hygiene;
- ≥3.1 – bad hygiene.

Study group

The study group included children aged 6–13 years, who were receiving orthodontic treatment as part of reim-

bursable care. Patients were treated with removable orthodontic appliances. A questionnaire was administered to 55 patients and their parents. A total of 60 copies were distributed among the patients' families. After verification, 55 correctly and fully completed questionnaires were accepted for analysis. There were 10 patients in the 6–7-year-old group, 15 patients in the 8–10-year-old group and 30 patients in the 11–13-year-old group.

Results

At visit 1, very good oral hygiene was found in a total of 6 (about 11%) patients, whereas poor oral hygiene was observed in 45.5% of patients, as shown in table 1.

A very good oral hygiene status was achieved in the group of the youngest patients (6 to 7 years of age). Importantly, 30% of parents in this group reported supervision or assistance during tooth brushing.

The level of hygiene declared by the parents is summarised in table 2. The analysis did not take into account patients age, but only the respondents' self-reported assessment. Only 10% of respondents declared very good oral hygiene, the same percentage declared poor hygiene. Most respondents reported moderate hygiene.

Attention was also paid to parental involvement in child's hygiene procedures, with particular emphasis on assisting the youngest children, as well as supervising them to evaluate the correctness and effectiveness of hygiene practices. The data are included in table 3.

In the youngest group, 10% of parents declared that they performed hygiene activities for their children. In the older groups of children (8–10 and 10–13 years of age), all patients performed hygiene activities on their own, and these were not verified by their parents. The use of additional oral hygiene tools, such as dental floss or mouthwash, was declared by a small percentage of respondents (15%).

At the second visit, during which the orthodontic appliances were provided to the patients, oral hygiene was again verified. The results are shown in table 4.

Table 3. Parental involvement in hygiene procedures performed by their children at visit 1

Parental involvement	Patient age (years)		
	6-7	8-10	11-13
Teeth brushed by the parent	10%	0%	0%
Teeth brushed by the child themselves	90%	100%	100%
Parental supervision of tooth brushing	30%	0%	0%
Parental control of brushed teeth	10%	0%	0%

Table 4. Oral hygiene at visit 2

Patient age (years)/number of patients in a group	Hygiene level % (n)			
	Very good	Good	Moderate	Bad
6-7/ 10 patients	20% (2)	20% (2)	40% (4)	30% (3)
8-10/ 15 patients	13.3% (2)	26.6% (4)	6.6% (4)	33.3% (5)
11-13/ 30 patients	13.3% (4)	20% (6)	30% (10)	30% (10)

Table 5. Parental involvement in hygiene procedures performed by their children at visit 2

Parental involvement	Patient age (years)		
	6-7	8-10	11-13
Teeth brushed by the parent	20%	0%	0%
Teeth brushed by the child themselves	80%	100%	100%
Parental supervision of tooth brushing	40%	13.3%	0%
Parental control of brushed teeth	50%	13.3%	30%

Table 6. Oral hygiene at visit 3

Patient age (years)/number of patients in a group	Hygiene level % (n)			
	Very good	Good	Moderate	Bad
6-7/ 10 patients	10% (1)	20% (2)	40% (4)	30% (3)
8-10/ 15 patients	13.3% (2)	20% (3)	33.3% (5)	33.3% (5)
11-13/ 30 patients	10% (3)	20% (6)	36.6% (11)	33.3% (10)

At the same visit, parental attitudes towards the children's hygiene procedures were assessed, with a particular focus on supervising and monitoring, as well as the child's participation in tooth brushing.

At the second follow-up visit, the parents reported greater involvement in their children's hygiene procedures. In the youngest group of patients (6-7 years), the percentage of parents performing tooth brushing for their child increased from 10% to 20%, which was not statistically significant ($p > 0.05$). In the older groups, on the other hand, the percentage of parents declaring verification of the effectiveness of these procedures increased and this change was statistically significant ($p < 0.001$). The results are presented in table 5.

Due to insufficient improvement in hygiene among the patients at their visit during which they received removable appliances, training on proper brushing technique was repeated. Both children and their parents were instructed on tooth brushing, and they were reminded of the importance of the duration and number of brushing sessions. The use of additional oral hygiene products such as mouthwash, dental floss, and educational toothpaste (to verify the effectiveness of hygiene procedures) was suggested.

The third visit, which took place 2 months after the onset of orthodontic treatment, was the endpoint of the study. The questionnaire procedure from the previous visits was repeated. The obtained data are shown in table 6. Good oral hygiene was found in 9 children at visit 1 compared to 11 children at visit 3. Although the number of children maintaining good hygiene increased, this change was not statistically significant ($p > 0.05$). Poor oral hygiene was reported in 25 patients at visit 1 and 18 patients at visit 3. This change was statistically significant ($p < 0.05$).

Children maintaining hygiene at a poor level were the largest group in all age categories. Despite two educational sessions and parental involvement in hygiene practices, patients maintaining hygiene at a very good level still accounted for the minority.

During the same visit, the parents were surveyed again to investigate their involvement in hygiene procedures and the level of supervision and control of their children's oral hygiene. The results are presented in table 7. It was shown that parents of the youngest children (6-7 years) maintained a similar level of assistance in their children's hygiene routines; however, they supervised and controlled their children's brushing less frequently compared to data from visit 2 and 3, which was a statistically significant change ($p < 0.05$), but at the same time they were more likely to control their children's hygiene behaviours compared to data from visit 1, which was not statistically significant ($p > 0.05$). In the older groups, there was an increase in the percentage of parents controlling their child's oral hygiene status, which was statistically significant ($p < 0.05$) compared to visit 1. Also in the older groups, a lower percentage of parents reported controlling the effectiveness of their children's hygiene procedures at visit 3.

Discussion

The study showed a significant correlation between the oral hygiene of orthodontic patients and plaque and biofilm accumulation. The effectiveness and regularity of hygiene procedures are crucial. Parental involvement, including control, supervision, and support in hygiene practices, is also an important factor, especially for younger patients. These observations are consistent with previous findings on orthodontically treated patients.

Table 7. Parental involvement in hygiene procedures performed by their children at visit 3

Parental involvement	Patient age (years)		
	6-7	8-10	11-13
Teeth brushed by the parent	20%	0%	0%
Teeth brushed by the child themselves	80%	100%	100%
Parental supervision of tooth brushing	20%	20%	0%
Parental control of brushed teeth	30%	33.3%	30%

Perzynski et al. conducted a study to assess the level of oral hygiene among patients undergoing orthodontic treatment [11]. Their conclusions are consistent with our study. They showed that oral hygiene among patients with orthodontic appliances was not maintained at an adequate level. In their conclusions, the authors emphasised the need to provide patients with individualised oral hygiene instructions.

The need to assess oral hygiene status in patients at various stages of orthodontic treatment has been pointed out in many studies [5, 8, 11–15]. Many authors also report frequent complications of orthodontic treatment in the form of gingivitis and intensified caries due to the lack of proper oral hygiene [16, 17].

Poor maintenance of oral hygiene combined with the use of orthodontic appliances results in an increased level of microorganisms, as demonstrated among others by Brzezińska-Zajac et al. Based on their observations, the authors concluded that long-term use of orthodontic appliances adversely affects the balance of microflora, contributing to the risk of dental caries and periodontal disease [18, 19].

Similarly, Volkan et al. assessed patients with space maintainers in their study and noted that these appliances contribute to an increased oral colonization with microorganisms and thus to an imbalance in the bacterial flora. They showed differences in this respect between fixed and removable appliances, emphasising the need for strict oral hygiene in patients treated with both types of devices [6].

A Polish study on oral hygiene in patients undergoing orthodontic treatment also reported difficulties in maintaining adequate hygiene [11].

Wites et al. surveyed patients about their oral hygiene habits, primarily in the context of manner and frequency at which they cleaned their teeth and orthodontic appliances. It was found that their oral hygiene was unsatisfactory, without correlation with the type of appliance used [20]. In the case of removable appliances, biofilm was more likely to be deposited directly on the device, whereas with fixed appliances, bacterial plaque deposition was more frequently observed on dental structures [3]. Słomska et al. found that hygiene procedures were unsatisfactory and irregular in 30% of patients. At the same time, the parents observed a deterioration in oral hygiene during treatment [18]. The authors concluded that failure to adhere to medical recommendations for hygiene procedures was the primary cause of oral infections in these patients. They also referred to parental attitude to educating and monitoring their children in

developing oral hygiene habits, and found that increased parental control of children's hygiene routines contributes to its improved effectiveness [18].

The results obtained by the aforementioned authors correspond with our observations. In our study, parental influence on the hygiene level of children was monitored at subsequent visits. The level of hygiene improved significantly in the group of younger children as a result of an adult performing hygiene activities such as tooth brushing. In the case of older children and adolescents, such an improvement was observed only after implementing oral hygiene control. At the same time, a decrease in hygiene levels was observed when parental assistance or supervision was discontinued.

Many authors emphasise the need to assess the oral status of orthodontic patients, especially during the initial months of treatment [19]. Similarly, many studies have pointed to the need for hygiene education of patients treated with orthodontic appliances [21]. Kozak and Dunin-Wilczyńska indicated that patients undergoing orthodontic treatment should be instructed on oral hygiene [12]. Many studies have shown the need for thorough oral hygiene instruction and frequent motivation of the patient to perform these procedures and to maintain proper oral hygiene throughout the orthodontic treatment process [21].

Our observations on oral hygiene are consistent with reports from around the world [17, 22, 23]. The same is true for parental involvement in the implementation of hygiene practices of their children. All studies demonstrate the need for increased oral hygiene in children undergoing orthodontic treatment and emphasise the value of parental involvement in the process of implementing the above practices.

Conclusions

- The study found a higher proportion of children with poor oral hygiene at baseline (first visit) in each age group, resulting in the need for providing oral hygiene instructions to both children and their parents.
- The parental role model and involvement in assisting, supervising and monitoring the outcomes of oral hygiene interventions is important for the quality and effectiveness of these interventions.
- Increased parental involvement translates into increased child involvement in maintaining good hygiene.
- Supervising hygiene procedures and controlling their effectiveness is particularly important in the group of patients aged 10–13 years, whereas lack of such involvement reduces the frequency and quality of these practices.

- For the youngest children (6–7 years), it seems more important to assist them with these procedures, e.g. tooth brushing, and to involve the parent in teaching the child appropriate behaviour.
- Observation of patients in the 6–13 age group treated with removable appliances confirmed the results from previous studies on the direct relationship between the use of removable appliances and the need for both increased oral hygiene and parental involvement in the process.
- The study focused on the use of removable appliances. Although it may seem that this type of treatment should pose no difficulties in maintaining oral hygiene, the results have shown that a significant proportion of patients failed to maintain satisfactory oral hygiene.

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RAPID SEQUENCE INTUBATION. THE CURRENT STATE OF KNOWLEDGE

Sekwencja szybkiej intubacji. Aktualny stan wiedzy



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Abstract

Rapid sequence intubation is a widely practiced method for handling the airway during anaesthesia induction in patients with gastric problems or those susceptible to regurgitation or aspiration. Preparation involves gathering essential equipment and medications for emergency intubation, including oxygen, suction, bag-valve mask, laryngoscope, endotracheal tubes with stylets, resuscitation gear, and rescue tools. Despite its consistent use for over five decades, debates persist regarding the efficacy of specific elements of the method, such as cricoid pressure and the assessment of fasting in urgent surgical cases. The absence of standardised rapid sequence intubation techniques and universally accepted guidelines has resulted in discrepancies in published data. Cricoid pressure, also known as the Sellick manoeuvre, is a controversial element of rapid sequence intubation that has both supporters and critics. While it has been used for decades and is recommended by many countries to prevent pulmonary aspiration during anaesthesia, recent research has raised questions about its effectiveness. In patients undergoing emergency surgery, ultrasound of the gastric antrum may help evaluate the size of gastric contents in order to minimise the risk of aspiration pneumonia. Techniques and variants of anaesthetic induction in the rapid sequence intubation algorithm should be adapted to a wide range of clinical groups – particularly in children, obese patients and pregnant women. In paediatric anaesthesia and for obese patients, the traditional rapid sequence intubation with apnoea is not commonly used due to their limited respiratory reserve. Despite its numerous side effects, succinylcholine remains the most frequently employed drug for rapid sequence intubation.

Streszczenie

Sekwencja szybkiej intubacji jest powszechnie stosowaną techniką zabezpieczania dróg oddechowych podczas indukcji znieczulenia u pacjentów ze schorzeniami żołądka, ryzykiem zarzucania treści pokarmowej do przełyku (regurgitacji) lub zachłyśnięcia (aspiracji). Procedura wymaga przygotowania sprzętu do szybkiej intubacji w trybie nagłym oraz leków: tlenu, ssaka, worka ambu z maską twarzową, laryngoskopu, rurek dotchawiczych z prowadnicą, zestawu do resuscytacji i niezbędnego sprzętu ratowniczego. Choć metoda jest wykorzystywana już od ponad 50 lat, nadal toczą się dyskusje na temat skuteczności niektórych jej elementów, takich jak ucisk na chrząstkę pierścieniową czy ocena stanu opróżnienia żołądka w nagłych wypadkach wymagających interwencji chirurgicznej. Brak ujednoczonych standardów dotyczących technik szybkiej intubacji oraz ogólnie przyjętych wytycznych postępowania prowadzi do rozbieżności w danych literaturowych. Ucisk na chrząstkę pierścieniową, zwany także manewrem Sellicka, jest kontrowersyjnym elementem szybkiej sekwencji intubacji, który ma zarówno swoich zwolenników, jak i przeciwników. Technika ta jest wprawdzie wykorzystywana już od kilkudziesięciu lat i zalecana w wielu krajach w celu zapobiegania aspiracji treści pokarmowej do płuc, jednak wyniki niedawnych badań wzbudziły wątpliwości co do zasadności jej stosowania. U pacjentów poddawanych zabiegom chirurgicznym w trybie nagłym badanie ultrasonograficzne żołądka może pomóc w ocenie objętości treści żołądkowej w celu zminimalizowania ryzyka zachłystowego zapalenia płuc. Metody i warianty indukcji znieczulenia w algorytmie szybkiej sekwencji intubacji wymagają dostosowania do specyfiki różnych grup klinicznych, zwłaszcza dzieci, osób otyłych i kobiet w ciąży. W znieczuleniu pediatrycznym i u pacjentów otyłych klasyczna szybka intubacja z okresem bezdechu nie jest powszechnie stosowana ze względu na ograniczoną rezerwę oddechową. Pomimo wielu działań niepożądanych lekiem najczęściej używanym w szybkiej sekwencji intubacji pozostaje suksametonium.

Keywords: rapid sequence induction and intubation; airway management; emergency treatment; complications

Słowa kluczowe: sekwencja szybkiej indukcji i intubacji; zarządzanie drogami oddechowymi; leczenie w nagłych przypadkach; powikłania

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Introduction

The RSI (“Rapid sequence intubation”, “Rapid sequence induction”, “Crush intubation”, “Crush induction”) is an airway management technique used for induction of anaesthesia in patients with gastric content or at risk of regurgitation or aspiration. The procedure is a special form of anaesthetic induction that has been a mainstay in clinical anaesthesia and emergency medicine for more than 50 years [1]. The components and sequence have remained the same for many years; the clinical value of cricoid pressure or even the assessment of fasting in patients with urgent surgical indications are topics of ongoing discussion [1, 2]. Other problems include the non-homogeneity of RSI techniques in the published data and the lack of internationally accepted RSI guidelines [1, 3].

Aim

The aim of the study was to discuss the induction of anaesthesia in the RSI algorithm in various clinical situations with particular emphasis on the role of ultrasound assessment and the Sellick manoeuvre.

Material and methods

The work is based on the available literature and the authors’ experience.

Results and discussion

Indications for rapid sequence intubation

Rapid sequence intubation is indicated for patients in acute respiratory failure due to poor oxygenation or ventilation, and for patients who cannot protect their airway due to altered mental status. RSI may also be used in patients with an acute upper gastrointestinal bleed at a high risk of aspiration. Absolute indications for RSI are presented in table 1 and relative indications in table 2.

Table 1. Absolute indications (classical rapid sequence induction) (Mencke et al.) [4]

Ileus and/or stenoses in the upper gastrointestinal tract
Acute abdomen
Wound disruption
Coma with concomitant multi-organ trauma
Emergency caesarean sections

Process of “classical” rapid sequence induction

“Classical RSI” consists of seven steps (7P) including preparation (monitoring of vital signs, intravenous line insertion, position of the patient before anaesthesia induction), preoxygenation, pretreatment (intravenous anaesthetic induction), paralysis with induction (an intravenous muscle relaxant drug with a rapid onset), protection and positioning (the Sellick manoeuvre), placement of the tube in the trachea, and postintubation management [5]. The main components of RSI are summarised in table 3.

Table 2. Relative indications (modified rapid sequence induction possible) (Mencke et al.) [4]

Patients with gastric content who have not fasted at least 6 hours after their last meal; however, there is no safe limit time for non-selective surgery
Obesity (body mass index ≥ 35 kg/m ²). Also applies to patients after bariatric surgery
Gastroesophageal reflux disease; this applies mainly to patients with symptomatic reflux and no Proton Pump Inhibitor therapy
Hiatal hernia and Zenker’s diverticulum
Gastropathy (diabetes, stage 5 chronic kidney disease, and liver failure)
Patients with painful injuries without multi-organ trauma

Table 3. Main components of “classical” Rapid Sequence Induction (Mencke et al.) [4]

Prepared workplace (environment and equipment)
Placement of gastric tube before induction of anaesthesia
Additional assistance
Elevation or lowering of the patient’s upper body by 30°
Removal of gastric tube before intubation
Preoxygenation (at least 3 min; alternatively 8 deep breaths over 60 s); effectiveness of denitrogenation can be monitored by end-expiratory oxygen concentration
Rapid application of anaesthetics
1.0 mg/kg succinylcholine (dosage according to absolute body weight) or at least 1.0–1.2 mg/kg rocuronium (dosage according to normal/ideal body weight)
No intermediate ventilation
In case of threatening hypoxia, cautious mask ventilation should be carried out (do not exceed a peak ventilation pressure of 15–20 cm H ₂ O); cricoid pressure should be considered
Endotracheal intubation with an intubating stylet
Insertion of a gastric tube

Preparation involves having all the necessary equipment and supplies including medications that may be needed for emergency intubation such as oxygen, suction, bag-valve mask, laryngoscope and blades, endotracheal tubes (ET) with a stylet with one size larger and smaller than the anticipated ET size, resuscitation equipment, and supplies for rescue manoeuvres (e.g. laryngeal mask airway or cricothyrotomy) [6].

Preoxygenation can be achieved in 3 to 5 minutes by having the patient breathe 100% oxygen via a tight-fitting facemask or, if time is limited, with four-eight vital capacity breaths. Positive pressure ventilation should be avoided during the preoxygenation step because of a risk for gastric aspiration and possible regurgitation. In the preoxygenation phase, replacing the nitrogen reservoir in the lungs with oxygen allows 3 to 5 minutes of apnoea without significant hypoxemia in the normoxic adult [7].

Muscle relaxants are a standard practice in the induction of anaesthesia in life-threatening conditions. Muscle relaxation in RSI has the advantage of significantly improving intubation conditions and reducing the need for intravenous anaesthetics, which prevents an increase in intracranial pressure. However, if intubation fails, there is a prolonged lack of spontaneous breathing, and the patient's life is threatened. A "can't ventilate, can't intubate" situation may also occur. It is also important to be aware of the numerous side effects of succinylcholine [8].

According to the standard procedure, the time for intubation is reached when the jaw becomes flaccid due to administration of paralytics. ET tube placement should be confirmed by the usual visualisation techniques.

Sellick manoeuvre

Cricoid pressure, also known as the Sellick manoeuvre, is an element of the RSI that has a high ratio of supporters and critics, but on the other hand has been well researched scientifically in recent years. The technique – first introduced by Sellick in 1961 – quickly established itself in everyday clinical practice – particularly in the United Kingdom. The pathophysiological effect is the closure of the oesophagus as it is pressed against the longus colli muscle rather than the cervical spine, because the oesophagus is displaced laterally rather than dorsally when the cricoid cartilage is compressed [9].

Although cricoid pressure has been used in clinical practice for decades, and it is recommended by most countries during RSI due to its effectiveness in preventing pulmonary aspiration, it may also have deleterious effects such as airway-related complications (interference with laryngeal exposure, difficult tracheal intubation and mask ventilation) [10]. In 2019, Birenbaum et al. conducted a large randomised, double-blinded clinical trial in patients undergoing anaesthesia with RSI, which failed to demonstrate the non-inferiority of a sham procedure as compared with cricoid pressure in preventing pulmonary aspiration. The researchers did not observe any significant differences in the occurrence of pneumonia, length of stay, and mortality [10].

It is important to remember that cricoid pressure may significantly worsen intubation conditions (higher grades 3 and 4 according to Cormack and Lehane in the "cricoid group"), resulting in longer intubation times. In RSI, where rapid and safe intubation is particularly important, this can be particularly problematic.

Additionally, it should be noted that optimal peak ventilation pressure should be 15–20 cm H₂O to avoid regurgitation [2].

In 2017, a study of the proper execution of the Sellick manoeuvre was carried out on a group of 206 doctors and nurses employed in Mazovian hospitals (Poland). Half of the respondents applied pressure to an incorrect area of the neck and the vast majority applied inappropriate force during compression. Therefore, the use of cricoid pressure in patients should be preceded by training on properly prepared trainees [11].

Crucially, laryngeal compression must be applied with the force necessary to cause oesophageal closure; this is 30 Newtons (N) (equivalent to 3.0 kg) for men and 20 N (equivalent to 2.0 kg) for women [12]. For educational purposes, a practical method to learn is by using a commercially available perfusion syringe filled with air to 50 mL and then squeeze it to 38 mL (20 N, women) or 33 mL (30 N, men) [13].

Gastric content and ultrasound

The aim of RSI is to prevent pulmonary aspiration which can lead to pneumonia and in the worst case to acute respiratory distress syndrome. A distinction is generally made between elective, urgent, and emergency surgery. In elective patients, it is sufficient to postpone the operation until a 6-hour fasting period has been achieved; in the absence of additional risk factors for pulmonary aspiration, the risk of aspiration remains unchanged. For emergency surgery, the risk of aspiration is usually increased even after 6 hours of fasting and affects at least 30% of all patients [2]. Ultrasound allows qualitative and quantitative assessment of the gastric antrum in patients who are still not fasting after 12 hours or more.

Several studies showed ultrasound as the most effective method for evaluating the gastric antrum. The probability of detecting the gastric antrum was 98%–100%. The right lateral position is the ideal position for scanning the antrum (with the highest sensitivity and specificity) because it is when the antrum is at the lowest point of the stomach [14]. The cross-sectional area (CSA) of the antrum can reflect the whole gastric volume (GV), and a remarkably positive correlation exists between CSA and GV [15]. Upon visualisation of the stomach during ultrasound, the gastric antrum has an ellipsoid shape, and the section area could be obtained by the antero-posterior (AP) diameter and craniocaudal (CC) diameter. The formula for estimating the risk of aspiration is [16]:

$$\text{Risk} = \frac{\text{CSA}}{\text{bodymass}} = \frac{\text{AP} \times \text{CC} \times 0,8}{\text{bodymass}}$$

The critical gastric volume associated with an increased risk of aspiration is still debatable. Healthy fasting patients regularly show a gastric volume of up to 1.5 mL/kg as basal gastric secretion, i.e., approximately 100 mL in a 70 kg patient [17]. Therefore, in the current recommendations, the cut-off is set at 1.5 mL/kg, i.e., if <1.5 mL/kg of clear fluid is found, the risk is low; if >1.5 mL/kg is found, the risk of aspiration is increased [14, 17]. Therefore, if no gastric fluid is found, the risk of aspiration is minimal.

Recent studies have shown that bedside ultrasound can provide reliable information about the volume and nature of gastric contents. With this technology, anaesthesiologists can make individual decisions to minimise the risk of perioperative aspiration. According to a 2020 study, routine ultrasound of the stomach in 100 patients led to a change in anaesthetic technique in nine cases (9%) [18].

Differences in rapid sequence intubation in specific clinical situations

In certain clinical circumstances, a modified technique is implemented in an attempt to optimise patient outcome and reduce excess risk exposure. Potential variations between the classic and modified RSI procedures include: (1) selection of a different neuromuscular blocking drug (NMBD); (2) timing of NMBD administration in relation to induction; (3) use of positive pressure ventilation before securing the airway; (4) timing of cricoid pressure application [19].

Rapid sequence intubation in children

The key features of a properly executed paediatric RSI include the avoidance of cricoid pressure, effective induction of sufficiently deep anaesthesia, and confirmation of complete muscle paralysis prior to tracheal intubation [20]. Intravenous access in “at-risk” patients is obtained as a standard practice. Intraosseous access represents a suitable alternative for children requiring resuscitation for emergency surgery and in whom intravenous access cannot be established [21].

Neonates, infants, and small children have a reduced apnoea tolerance in comparison with adults. A direct consequence is that hypoxaemia is very likely to occur in the period between the induction of anaesthesia and re-establishment of ventilation through the tracheal tube during a “classic” RSI. Therefore, to avoid hypoxemia and hypercapnia, it is important to use gentle ventilation, which includes the use of a pressure-limited mask ventilation with 100% oxygen for 4 minutes and with pressures not exceeding 10–12 cm H₂O [22].

Subjective sense of thirst or hunger cannot be used as a reliable method to judge the quantity of gastric contents, and bedside ultrasound is the only non-invasive technique to estimate gastric volume in infants. Recent research indicates that the previously recommended fasting time might be too conservative, while ultrasonography before anaesthesia plays an important role in assessing the risk of aspiration in paediatric patients [23].

Rapid sequence intubation for caesarean sections

Pregnant women have a threefold higher risk of aspiration compared to other patients, which has been reported in the literature. This may be due to increased gastric pressure in late gestation [24]. In addition, mortality after aspiration is significantly higher compared to non-pregnant adult patients (3.5% vs. 12%) [25]. Among many other factors, the shift from general anaesthesia to regional procedures near the spinal cord in obstetrics has significantly reduced maternal mortality in recent decades [26]. Also for this reason, the regional procedure without additional sedation is used in patients who are at risk of aspiration.

General anaesthesia in the context of caesarean section is currently reserved mainly for emergency sections or where central blocks have been technically unsuccessful or are contraindicated. This is because approximately 1–2% of maternal deaths can be directly or indirectly attributed to anaesthesia [23]. In elective or active emergency incisions, prevention of aspiration includes the administration of an H₂-receptor antagonist 60 min before surgery, possibly with the addition of metoclopramide. In emergency surgery, an antacid is administered orally prior to incision (0.3 mol sodium citrate 30 mL) [27]. Of the intravenous anaesthetics, thiopental has historically been used for the induction of anaesthesia, and it is still often the drug of choice, although propofol may be a better alternative. There are no supplementary recommendations for opioids and muscle relaxants, as well as the use of the Sellick manoeuvre and airway management [3]. An opioid can be given in a low dose for induction, this is typically done only after the baby has been extracted [25].

Rapid sequence intubation in obese patients

In morbidly obese patients, RSI or fast intubation is still considered the preferred method of induction to general anaesthesia, except for expected difficult airways, where fibre optic intubation is better [28]. In addition, dosing medications based on total body weight may lead to overdose in obese patients, whereas dosing based on ideal body weight may lead to underdosing. According to a retrospective review, obese patients undergoing RSI in the ED were more likely to be underdosed with both etomidate and succinylcholine [29]. For obese patients, a dose of 1.5 mg/kg seems to be required – according to absolute or (note) actual body weight. Improper dosing of medications for RSI has the potential to lead to prolonged paralysis or suboptimal intubating conditions. It can be particularly detrimental given the challenges associated with airway management in obese patients, including more difficult mask ventilation and more rapid desaturation during apnoea. Since obesity is an independent risk factor for full stomach, and airway management may be difficult in these patients, preoperative gastric ultrasound is recommended to assess the risk of aspiration [29].

Pre-treatment strategies

Pre-treatment agents are medications given before starting RSI to lessen the potential negative physiological responses, like high blood pressure and rapid increases

in intracranial pressure. Despite their potential benefits, there is limited evidence linking their use to better patient outcomes, and they are not commonly used in clinical practice. Atropine, lidocaine, and fentanyl are commonly mentioned as pre-treatment agents, and they are ideally administered 2–3 minutes before induction to allow for their desired effects. Atropine, derived from belladonna, acts as a competitive antagonist to acetylcholine, boosting the heart rate by blocking vagus nerve signals. This counters bradycardia during intubation, especially in children. Despite recommendations, evidence supporting its routine use is limited. A recent study on 62 paediatric patients found that bradycardia rates were similar with or without atropine (4.3% vs. 6.6%). The recommended dose for pre-treatment is 0.01 mg/kg in adults and 0.02 mg/kg in paediatrics, with a typical maximum of 0.5 mg. Historical concerns of paradoxical bradycardia for doses <0.1 mg lack strong evidence, and overall, the benefit of atropine in preventing bradycardia, even in high-risk cases, remains uncertain. Lidocaine, a sodium channel blocker categorised as an antiarrhythmic class 1B and local anaesthetic, demonstrates multiple effects when administered intravenously, such as bronchodilation, cough suppression, and potential reduction in ICP, intraocular pressure, and MAP during intubation. In the context of RSI, lidocaine is utilised to counteract a surge in catecholamines, particularly in traumatic brain injury (TBI) patients. Despite these potential benefits, there is a lack of robust data supporting lidocaine's efficacy for this purpose. Lidocaine is believed to mitigate ICP increases resulting from coughing during RSI, potentially benefiting TBI patients. However, studies demonstrating lidocaine's cough suppression ability did not involve neuromuscular blocking agents (NMBA). To date, no study has shown significant differences in ICP reduction when lidocaine is administered for cough suppression during traditional RSI, and there is limited evidence of direct ICP reduction. Additionally, lidocaine is thought to prevent bronchoconstriction resulting from airway stimulation during intubation, especially in asthmatic individuals. However, research findings on this topic are inconsistent. The historically recommended dose for lidocaine pre-treatment is 1.5 mg/kg, with the peak effect on ICP observed two minutes after administration. Adverse effects include hypotension and bradycardia, mainly at higher plasma levels, beyond typical RSI dosing. Due to contradictory and generally low-quality data, the use of lidocaine for pre-treatment is discouraged. Fentanyl, a short-acting synthetic opioid often suggested as a pre-intubation treatment, aims to dampen the heightened sympathetic response to pain during laryngoscopy. Theoretically, by countering the pain-induced increase in mean arterial pressure (MAP), complications in patients with compromised cerebral autoregulation, acute coronary syndromes, and aortic dissection can be prevented. Fentanyl acts rapidly, with an effect duration of about 60 minutes. While historically used to lower MAP in traumatic brain injury (TBI), subsequent decreases in MAP post-intubation can negatively impact cerebral perfusion pressure (CPP), posing a concern for TBI patients. However, the varied findings and a lack of real-world, patient-centred clinical outcomes data hinder the widespread use of fentanyl for pre-treatment in RSI among TBI patients. Notably, guidelines for TBI management do not endorse its use. The historically recommended dose for

fentanyl pre-treatment exceeds typical analgesic dosing (3 µg/kg). Smaller doses (e.g. 1 µg/kg) can be synergistically used with midazolam to reduce induction agent requirements. Adverse effects encompass hypotension and respiratory depression, with high doses posing a risk of accelerated respiratory depression. Chest wall rigidity, a rare complication often associated with higher doses, is unlikely with pre-treatment doses administered over 60 seconds. While fentanyl effectively lessens MAP increases during intubation in the operating room, its use in RSI is linked to post-intubation, dose-dependent hypotension in the emergency department. Considering the available literature, the potential benefits of blunting MAP increases during intubation do not outweigh the risk of post-intubation hypotension [30].

Conclusions

A modified RSI is used to prevent the occurrence of pulmonary aspiration. The classic RSI, including apnoea, is not implemented in paediatric anaesthesia, as is the case in the anaesthesia of obese patients. This is due to the lack of respiratory reserve in patients in these two clinical groups. Succinylcholine is most commonly used for RSI despite its numerous side effects; rocuronium is an alternative but a high dose is needed and Sugammadex protection is then required. Absolute indications for RSI include all gastrointestinal obstructions. Pre-treatment agents, administered before RSI, aim to alleviate adverse physiological responses. Despite their potential advantages, their use lacks robust evidence for enhancing patient outcomes, and they are not widely embraced in clinical practice.

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INTESTINAL PARASITIC INFECTIONS AMONG UKRAINIAN CHILD WAR REFUGEES LIVING IN WARSAW

Zarażenia pasożytami jelitowymi u dzieci ukraińskich – uchodźców wojennych mieszkających w Warszawie



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Abstract

Introduction and objective: The war and the humanitarian crisis in Ukraine have resulted in a mass migration of millions of Ukrainians into the EU countries. According to the data obtained from Statistics Poland, a governmental agency collecting and publishing the country's statistical data, the number of Ukrainian children currently living in Poland is approximately 500,000. The massive influx of immigrants into Poland poses a considerable challenge to the national health care sector. The aim of this study was to assess the prevalence of intestinal parasitic infections among Ukrainian child war refugees living in Warsaw. **Material and methods:** The study involved a total of 25 Ukrainian children, patients of the Clinic of Paediatrics, Nephrology and Paediatric Allergology at the Military Institute of Medicine – National Research Institute in Warsaw. Parasitological diagnostic work-up was carried out in October 2023 at the Department of Epidemiology and Tropical Medicine, the Military Institute of Medicine – National Research Institute in Gdynia. Stool tests for the presence of intestinal parasites were conducted by light microscopy using three different methods (direct smear in Lugol's solution, decantation with distilled water, Fülleborn's flotation). **Results:** A total of 20% of the children studied (5/25) were found to be infected with potentially pathogenic stramenopile *Blastocystis* spp. In addition, two of the children were also infected with non-pathogenic *Endolimax nana* and *Entamoeba coli* protozoa. There were no infections with nematodes, cestodes or trematodes among the study participants. **Conclusions:** The confirmation of potentially pathogenic *Blastocystis* spp. in stool samples collected from Ukrainian children, war refugees living in Warsaw, justifies the necessity to re-introduce a large-scale routine screening for intestinal parasites in the paediatric population in Poland.

Streszczenie

Wstęp i cel: Wojna i kryzys humanitarny w Ukrainie wywołały masową migrację milionów Ukraińców do krajów Unii Europejskiej. Z danych polskiego Głównego Urzędu Statystycznego – organu administracji rządowej odpowiedzialnego za prowadzenie badań statystycznych – wynika, że aktualnie na terytorium Polski przebywa około 500 000 ukraińskich dzieci. Masowy napływ imigrantów do Polski stanowi spore wyzwanie dla krajowego systemu ochrony zdrowia. Celem pracy była ocena częstości występowania zarażeń pasożytami jelitowymi wśród mieszkających w Warszawie ukraińskich dzieci – uchodźców wojennych. **Materiał i metody:** Do badania włączono 25 ukraińskich dzieci, pacjentów Kliniki Pediatrii, Nefrologii i Alergologii Dziecięcej Wojskowego Instytutu Medycznego – Państwowego Instytutu Badawczego w Warszawie. Diagnostykę parazytologiczną przeprowadzono w październiku 2023 r. w Zakładzie Epidemiologii i Medycyny Tropikalnej Wojskowego Instytutu Medycznego – Państwowego Instytutu Badawczego w Gdyni. Badania kału na obecność pasożytów jelitowych wykonano w mikroskopii świetlnej z wykorzystaniem trzech różnych metod (rozsmazu bezpośredniego w płynie Lugola, dekantacji w wodzie destylowanej, flotacji metodą Fülleborna). **Wyniki:** U 20% (5/25) dzieci z badanej grupy stwierdzono zarażenie potencjalnie patogennymi stramenopilami z rodzaju *Blastocystis* spp. Dwoje dzieci było zarażonych także niepatogennymi pierwotniakami *Endolimax nana* i *Entamoeba coli*. Wśród uczestników badania nie stwierdzono przypadków zarażeń nicieniami, tasiemcami ani przywrami. **Wnioski:** Potwierdzenie obecności potencjalnie chorobotwórczych organizmów z rodzaju *Blastocystis* spp. w próbkach kału pobranych od mieszkających w Warszawie dzieci ukraińskich – uchodźców wojennych wskazuje na potrzebę ponownego wprowadzenia szeroko zakrojonych rutynowych badań przesiewowych na obecność pasożytów jelitowych w populacji pediatrycznej w Polsce.

Keywords: children; intestinal parasites; Ukraine; war refugees

Słowa kluczowe: dzieci; pasożyty jelitowe; Ukraina; uchodźcy wojenni

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Introduction

The war and the humanitarian crisis in Ukraine have resulted in a mass migration of millions of Ukrainians into the EU countries, mainly to Poland. More than three million Ukrainian war refugees crossed to Polish border in the early days of the Russian invasion. A year and a half after the invasion, more than one million Ukrainians remain in Poland, enjoying temporary protection. According to the data made available by Statistics Poland, half of those refugees are children [1]. The massive influx of immigrants into Poland poses a considerable challenge to the national public health care sector [2]. The hardships associated with travel and dislocation, coupled with migration-related stress, poor sanitation, immunodeficiency, and insufficient vaccination coverage among Ukrainian children, are the major factors contributing to the risk of transmission of infectious diseases [3]. A study carried out in a group of child war refugees found that the key health issues included tuberculosis, hepatitis A, B and C, and parasitic diseases [4]. It is currently impossible to determine the epidemiological status of parasitic infections in Ukraine (except for giardiasis and cryptosporidiosis), as there is no obligation to notify the state's authorities of new cases of most intestinal parasitic diseases. The situation is similar in Poland. The reports published by the Ministry of Health of Ukraine include information on the infection rates of the two above-mentioned protozoan diseases only, without providing any information on the prevalence of other intestinal parasites. Findings from the last two years demonstrate a sharp increase in the number of cases of intestinal protozoan infections in Ukraine, from 2,396 cases reported in 2022 to as many as 3,836 cases reported in the first nine months of 2023 [5]. The data may, however, be significantly under-reported because of the limited diagnostic capacity of the laboratories operating in Ukraine (which is associated with the ongoing war). A massive influx of war refugees from Ukraine into Poland justifies the introduction of a health assessment programme for Ukrainian refugees, especially the paediatric population. The aim of this study was to determine the prevalence of intestinal parasitic infections among Ukrainian child war refugees living in Warsaw.

Materials and methods

The study involved a total of 25 Ukrainian children, patients of the Clinic of Paediatrics, Nephrology and Paediatric Allergology at the Military Institute of Medicine – National Research Institute in Warsaw. Medical history of the patients was obtained by a consulting physician.

The medical history included information on the patients' age, sex, place of residence in Ukraine, a history of any gastrointestinal symptoms, and the use of any antibiotics or antiparasitic drugs during the three months before the visit. Three stool samples were collected from each study participants at intervals of 2–3 days. The samples were fixed with SAF (sodium acetate – acetic acid – formalin) and transported to the Department of Epidemiology and Tropical Medicine at the Military Institute of Medicine – National Research Institute in Gdynia for parasitological examination. The samples were tested by three different light microscopy methods (direct smear in Lugol's solution, decantation in distilled water, and Fülleborn's flotation) [6, 7]:

Direct smear in Lugol's solution

Approximately 2 mg of stool was collected with a glass rod and applied onto a slide. A drop of Lugol's solution was added, and the material was smeared over a 4 cm² surface. Next, a cover slide was placed on top of the preparation, and the specimen was examined microscopically at ×20 magnification.

Decantation with distilled water

Approximately 2 mL of stool sample was mixed thoroughly with a small amount of water in a test tube. Next, water was added to the top of the tube and mixed again. After 30 minutes, the supernatant was decanted, and another portion of water was added. This procedure was repeated until clear supernatant was obtained, usually three to four times. The sediment was then placed on a slide, stained with Lugol's solution, and examined microscopically at ×40 magnification.

Fülleborn's flotation

Approximately 2 mL of stool specimen was mixed with saturated NaCl solution in a test tube. Next, NaCl solution was added to the top of the tube. A cover slide was placed on the top of the tube and in contact with the suspension. After 30 minutes, the cover slide was gently removed with tweezers and placed the wet side down on a slide. The preparation was thus ready for microscopic examination at ×10 magnification.

Ethical considerations

Each parent/legal guardian submitted an informed written consent for their child to participate in the study and

to be screened for intestinal parasites by researchers from the Clinic of Paediatrics, Nephrology and Paediatric Allergology at the Military Institute of Medicine – National Research Institute in Warsaw, Poland. They were also requested to provide their child's personal details and medical history. The information clause on personal data processing by the Military Institute of Medicine – National Research Institute, Warsaw, Poland was drawn up pursuant to Article 14 (1) and (2) of the Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, hereinafter referred to as General Data Protection Regulation (GDPR).

Results

Intestinal parasites were found in five out of 25 Ukrainian children living in Warsaw. All infections were caused by potentially pathogenic stramenopile *Blastocystis* spp. There were two cases of co-infection with non-pathogenic *Entamoeba coli* and *Endolimax nana*; no infections with nematodes, cestodes or trematodes were detected (tab. 1).

The information obtained during the initial visit by a consulting paediatrician demonstrated that 60% of the infected children had reported gastrointestinal symptoms, including abdominal pain, nausea, vomiting, weight loss, diarrhoea or constipation. Positive cases were most common among girls (4/5) of the primary school age (6–13 years old) and in children coming from Western Ukraine (4/5). Of all the examined children, three were taking antimicrobial or antiparasitic drugs during the three months preceding the enrolment in the study, with one child diagnosed with a *Blastocystis* spp. infection (tab. 2).

Discussion

According to the UN reports, the total number of child migrants globally is approximately 31 million, including 13 million child refugees or asylum seekers. Children are at a particularly high risk of developing intestinal parasite infections due to poor personal hygiene practices and a tendency to geophagia. This, coupled with migration-related stress and difficulties experienced while travelling from one country to another, significantly increases the risk of an infection in the paediatric population [8, 9].

Table 1. Intestinal parasitic infections in Ukrainian children living in Warsaw (n = 25)

Intestinal parasitic infections	n	%
Negative (-)	20	80
Positive (+)	5	20
<i>Blastocystis</i> spp.	3	12
<i>Blastocystis</i> spp. + <i>Entamoeba coli</i>	1	4
<i>Blastocystis</i> spp. + <i>Endolimax nana</i>	1	4
Nematodes	-	-
Cestodes	-	-
Trematodes	-	-

According to the data from the American Academy of Paediatrics, stool tests for ova and parasites give positive results in 15–35% child-migrants, depending on the country of origin and the age of the child [10]. In the present study, the overall infection rate with parasites was 20%, which is in line with the findings published by Bustamente et al. [11] and Manganelli et al. [12]. Both studies focused on child-migrants whose parents were of European descent. The infection rate reported by the two authors was 25% and 14.9%, respectively. There were no cases of helminth infections in any of the two study groups, which is similar to the findings of the study which involved of a group Ukrainian children adopted abroad [13]. The present study found that all the infections (100%) were caused by *Blastocystis* spp. There were two cases of co-infection with *Blastocystis* spp. and non-pathogenic *Entamoeba coli* or *Endolimax nana* protozoa. The parasites found in the samples collected from the study participants are quite common in Poland [14–16]. A number of studies which involved European children confirm the fact that most parasitic infections seen in Europe are caused by protozoa [17–19]. According to the data from the Ministry of Health of Ukraine, there was a considerable decrease in the number of infections caused by intestinal parasites (especially helminthiasis) in Ukraine between 1984 and 2020. The reduction in the number of parasitic infections among Ukrainians was largely due to the widespread use of anti-parasitic drugs in the country, but it could also be associated with limited diagnostic capabilities of the laboratories operating in Ukraine (between 1984 and 2020, the number of stool tests fell by around 20 million) [5]. The findings of the studies carried out between 1995 and 2016 at the Institute of Epidemiology and Infectious Diseases at the National Academy of Medical Sciences of Ukraine suggest that the rate of intestinal infections caused by potentially

Table 2. Intestinal parasitic infections in Ukrainian children living in Warsaw (n = 25)

Ukrainian children	n	Parasitic infections (+) positive	Parasitic infections (-) negative
	25 (100%)	5 (20%)	20 (80%)
Sex			
Female	16 (64%)	4 (16%)	12 (48%)
Male	9 (36%)	1 (4%)	8 (32%)
Age			
<6	9 (36%)	1 (4%)	8 (32%)
6–13	9 (36%)	3 (12%)	6 (24%)
>13	7 (28%)	1 (4%)	6 (24%)
Region of Ukraine			
West	7 (28%)	4 (16%)	3 (12%)
East	9 (36%)	1 (4%)	8 (32%)
North	5 (20%)	0	5 (20%)
South	4 (16%)	0	4 (16%)
Gastrointestinal symptoms (last 3 months)			
Yes	10 (40%)	3 (12%)	7 (28%)
No	15 (60%)	2 (8%)	13 (52%)
Antibiotic or antiparasitic drugs (last 3 months)			
Yes	3 (12%)	1 (4%)	2 (8%)
No	22 (88%)	4 (16%)	18 (72%)

pathogenic parasites continues to grow in Ukraine [20, 21]. A similar trend has been observed by Lebanese researchers, who found that the detection rates of *Blastocystis* spp. in stool samples increased from 0% in 1997–1998 to 17% in 2007–2008 [22]. A total of 60% of the children enrolled in the present study reported gastrointestinal symptoms. The pathogenic role of *Blastocystis* spp. is not yet fully understood. Although it is widely regarded as a commensal parasite [23, 24], there have been reports suggesting that *Blastocystis* spp. infection may be responsible for symptoms such as nausea, flatulence, abdominal pain, acute or chronic diarrhoea [25–27]. What is more, Zaman et al. [28] observed a significant correlation between the presence of asymptomatic *Blastocystis* spp. infestation and the risk of dwarfism in children. This observation should prompt routine stool testing in the paediatric population in order to prevent the possible long-term effects of the asymptomatic carriage of *Blastocystis* spp. The present study showed that parasitic infections were most common among school-age children, which is consistent with the observations made by other authors [29, 30]. The reason for increased rates of parasitic infections in this age group may include poor toilet and food hygiene. Since pre-school children are normally supervised by their parents/guardians while using the toilet or eating, the risk of exposure to parasitic infections in this age group is usually lower. The present study also found that parasitic infections were more common in girls compared to boys, although other researchers have not observed or reported of a correlation between gender and the rate of infections with intestinal parasites [27, 31]. The limitation of the present study was its small sample size ($n = 25$), which made it difficult to analyse the correlation between variables such as age and sex of the participants or the presence/absence of clinical signs. However, despite the relatively small number of participants, the study results clearly showed the predominance of infections with *Blastocystis* spp. Due to the possible negative long-term effects of asymptomatic *Blastocystis* spp. carriage, it is recommended to introduce regular screening of the paediatric population for parasites. In Poland, there is no obligation to report new cases of most intestinal parasitic diseases. In addition, Poland no longer conducts regular childhood screening for parasitic diseases, which makes it extremely difficult to determine the actual rates of parasitic diseases. The epidemiological situation in Ukraine is, in fact, very similar to the one in Poland. In both countries, giardiasis and cryptosporidiosis are the only notifiable gastrointestinal parasitic diseases [6, 16]. The reports confirming a high prevalence of *Blastocystis* spp. infections among European children justify the need to re-introduce routine screening for intestinal parasites in Poland.

Conclusions

The confirmation of potentially pathogenic *Blastocystis* spp. in stool samples collected from Ukrainian children, war refugees living in Warsaw, justifies the necessity to re-introduce a large-scale routine screening programme for intestinal parasites in the paediatric population in Poland.

Conflict of interest statement

Authors declare no conflict of interest in relation to this article.

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ANALYSIS OF DIFFERENCES IN THE CONCENTRATION OF ANTI-SARS-COV-2 ANTIBODIES IN THE COURSE OF COVID-19 DEPENDING ON DISEASE SEVERITY, SEX, AGE, AND VACCINATION STATUS



Analiza różnic w stężeniu przeciwciał przeciw SARS-CoV-2 w przebiegu COVID-19 w zależności od ciężkości choroby, płci, wieku i statusu szczepienia

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Abstract

Introduction and objective: The role of immunoglobulin G antibodies in combating SARS-CoV-2 infection, modulation of COVID-19 disease severity, and persistence of humoral response after primary infection and vaccination is unclear. This study aimed to evaluate the role of antibodies in limiting the infection, modulating disease severity, and determining the durability of the immune response depending on the clinical status of patients, their age, sex, and vaccination status. **Material and methods:** The study involved 156 patients, 99 men and 57 women, aged 58.3 ± 12.5 years old, hospitalised for pneumonia in the course of COVID-19, with infection confirmed by real-time polymerase chain reaction test. The concentration of anti-SARS-CoV-2 IgG antibodies was tested at 3, 6, and 9 months from the day of hospitalisation. **Results:** The concentration of anti-SARS-CoV-2 IgG antibodies in patients with severe COVID-19 was higher compared to the group of patients with mild to moderate disease. The level of anti-SARS-CoV-2 IgG antibodies was comparable in men and women. In patients over 60 years of age, a lower concentration of antibodies was observed than in patients under 60 years of age. In the vaccinated group, the level of antibodies was higher than in the unvaccinated group. **Conclusions:** The study findings showed that the concentration of IgG anti-SARS-CoV-2 antibodies was not a parameter dependent on the sex of the patients, but rather on the severity of the disease and the age of the patients and their vaccination status.

Streszczenie

Wstęp i cel pracy: Rola immunoglobuliny G w zwalczaniu ostrej niewydolności oddechowej wywołanej zakażeniem SARS-CoV-2, modulacji ciężkości COVID-19 i utrzymaniu odpowiedzi humoralnej po pierwotnym zakażeniu i szczepieniu nie jest jasna. Celem pracy była ocena roli przeciwciał w ograniczaniu zakażenia, modulacji ciężkości choroby i odpowiedzi immunologicznej w zależności od stanu klinicznego pacjentów, ich wieku, płci i statusu szczepienia. **Materiał i metody:** Badaniem objęto 156 pacjentów, w tym 99 mężczyzn i 57 kobiet, w wieku $58,3 \pm 12,5$ roku, hospitalizowanych z powodu zapalenia płuc w przebiegu COVID-19, z zakażeniem potwierdzonym testem łańcuchowej reakcji polimerazy w czasie rzeczywistym. Stężenie przeciwciał IgG przeciw SARS-CoV-2 badano w miesiącach 3., 6. i 9. od dnia hospitalizacji. **Wyniki:** Stężenie przeciwciał IgG przeciwko SARS-CoV-2 u pacjentów z ciężką postacią COVID-19 było wyższe w porównaniu z grupą pacjentów z łagodną i umiarkowaną postacią choroby. Stężenie przeciwciał IgG przeciw SARS-CoV-2 było porównywalne u mężczyzn i kobiet. U pacjentów powyżej 60. roku życia obserwowano niższe stężenie przeciwciał niż u pacjentów poniżej 60. roku życia. W grupie zaszczepionej stężenie przeciwciał było wyższe niż w grupie niezaszczepionej. **Wnioski:** Przeprowadzone badania wykazały, że stężenie przeciwciał IgG przeciw SARS-CoV-2 nie jest parametrem zależnym od płci, ale raczej od ciężkości choroby, wieku pacjentów i ich statusu szczepienia.

Keywords: vaccination; antibodies; SARS-CoV-2

Słowa kluczowe: szczepienie; przeciwciała; SARS-CoV-2

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Introduction

The first case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was officially confirmed on 1 December 2019 in Wuhan, China, [1]. The rapidly spreading virus caused COVID-19 disease in 757,264,511 individual cases, of which 6,850,594 were fatal [1]. The introduction of vaccination (13,220,848,592 vaccinated individuals [2]), as well as the rise of population immunity developed through infection, made it possible to eventually slow down the pandemic. Nevertheless, complete eradication of SARS-CoV-2 was not possible. It is believed that the virus, similarly to other coronaviruses or influenza viruses, will cause recurrent outbreaks of varying morbidity. These fluctuations in prevalence depend on many factors, such as the adoption of restrictions by affected communities and effective epidemiological surveillance. One of the indicators of population immunity to infectious diseases is the assessment of the titre of the immunoglobulin G (IgG) antibodies. In the case of SARS-CoV-2, the available data is insufficient to unequivocally state that the analysis of the concentration of anti-SARS-CoV-2 antibodies is directly associated with the acquisition of natural and post-vaccination immunity. Current data on the role of antibodies in combating infections, modulation of COVID-19 severity, and the persistence of humoral response after primary infection and vaccination is either limited or controversial [3–5].

Most individuals infected with SARS-CoV-2 develop antibodies against spike (S) and nucleocapsid (N) proteins, which are also used in clinical serological tests [6]. The spike protein is an important target for neutralising antibodies. The combination of these antibodies with the S protein of the virus can effectively prevent the virus from entering the host cells [7, 8]. Seroconversion for the IgM antibodies usually occurs within 5 days of the onset of symptoms, and seroconversion for the IgG antibodies – within 7 days. Depending on the method used and individual variability, seroconversion can be observed after a median time of 10–13 days from the onset of symptoms in the case of IgM antibodies and 12–14 days in the case of IgG antibodies [9]. Maximum seroconversion occurs within 2–3 weeks for IgM antibodies, 3–6 weeks for IgG antibodies, and 2 weeks for all antibodies. While IgM antibodies tend to disappear at around 6–7 weeks, high IgG seropositivity is observed at the same time. Reports on the persistence of SARS-CoV-2 antibody titres are not fully consistent, with some finding a rapid decline in virus-specific IgG antibodies approximately 3 months after infection, and others highlighting stable titres detected more than a few weeks or even months post infection [10–14].

The concentrations and chronological order of appearance of IgM and IgG antibodies are highly variable, which

provides the basis and justification for the parallel detection of both these antibodies. The time of seroconversion following stimulation of humoral response by the administration of the vaccine seems to coincide with the natural process of appearance of anti-SARS-CoV-2 antibodies after infection. From the currently available studies, it can be concluded that messenger Ribonucleic Acid (mRNA) vaccines induce a higher titre of IgG antibodies after 1 and 2 doses compared to traditional vaccines [15–17]. Nevertheless, this data does not indicate the greater effectiveness of mRNA vaccines. The present study is an analysis of anti-SARS-CoV-2 antibody concentrations in individuals with COVID-19 during their hospitalisation and convalescence. The study was conducted to evaluate the role of antibodies in limiting the infection, modulating the disease severity, and determining the durability of the immune response depending on the clinical status of patients, their age, sex, and vaccination status.

Material and methods

This study involved 156 individuals, including 99 males and 57 females, aged 58.3 ± 12.5 years old, diagnosed with pneumonia in the course of COVID-19, with or without symptoms of acute respiratory failure, and hospitalised at the Military Institute of Medicine – National Research Institute (MIM-NRI Poland) between January and November 2021.

Patients with COVID-19 who met the following criteria were included in the study:

- presence of SARS-CoV-2 infection confirmed with real-time polymerase chain reaction (PCR);
- pneumonia confirmed with computed tomography;
- passive oxygen therapy required;
- high-flow oxygen therapy or ventilator therapy required.

All the individuals were informed about the purpose of the study and gave their informed consent to participate. The consent of the local Bioethics Committee was also obtained. An additional study group was established, consisting of 67 individuals vaccinated against COVID-19 after their symptoms completely subsided.

Peripheral blood samples of 8 mL per draw were collected by venipuncture into the cubital fossa at 3, 6, and 9 months from the day of initial hospitalisation. The blood samples were centrifuged at 3,000 rpm for 5 minutes at room temperature, and the obtained serum was frozen and stored at -25°C . The determination of anti-SARS-CoV-2 antibodies was performed using an IgG and IgM antibody quantification kit by ELISA. The determination of the antibody titre was performed in serum using the COVID-19 ELISA IgM + IgA and COVID-19 ELISA IgG kits by Vircell Microbiologists (Spain) on the Dynex Magellan Biosciences sys-

tem. The test was targeting anti-SARS-CoV-2 antibodies against S protein. The results were read using DS-Matrix 1.40.3. Each subject had the presence of the SARS CoV-2 virus confirmed by the Real-Time PCR test using Gene-Finder™ COVID-19 Plus RealAmp Kit (Korea) reagents on the Bioer LineGene 9600 Plus system.

Statistics

The data obtained during the study were of three types: range (age, time points of the study), ordinal (assessment of the clinical condition), and nominal (sex, vaccination status – vaccinated or unvaccinated). Because the study groups were markedly unequal in size, the statistical analysis was performed with the Wilcoxon test. Differences between the variables were considered significant when the level of significance p was lower than $1-\alpha = 0.05$ for the obtained test value.

Results

Comparison of the presence of the IgG anti-SARS-CoV-2 antibodies between groups with mild to severe course of the disease

The 156 individuals included in the study were divided into two groups according to the severity of respiratory insufficiency. The criterion was the introduction of oxygen therapy:

- Group I included patients with a mild to moderate course of the disease – 136 individuals who required passive oxygen therapy with the use of nasal cannulas, simple face masks, and non-rebreather face masks; 66 individuals from this group completed the study.
- Group II included patients with a severe course of the disease – 18 individuals requiring high-flow oxygen therapy (with the use of HFNC-High Flow Nasal Cannula) or ventilator therapy; three individuals from this group completed the study.

The median concentration of the IgG antibodies in group II was 1,000 IU/mL, while in group I, the median concentration was 730.5 IU/mL, which constitutes a statistically significant difference ($p = 0.012$). In individuals with a severe course of the disease at months 3, 6, and 9 of the study, the median IgG antibody concentrations remained high at 1,371.1 IU/mL; 1,137.3 IU/mL; and 1,435.2 IU/mL, respectively. These differences were found to be statistically insignificant.

To compare, the median concentration of the IgG antibodies in group I at months 3, 6, and 9 of the study, was found to increase, constituting a statistically significant difference ($p < 0.001$), and amounted to 1,196.0 IU/mL; 1,225.5 IU/mL; and 1,265.1 IU/mL, respectively.

Table 1 presents changes in the concentrations of the IgG anti-SARS-CoV-2 antibodies between the groups of mildly, moderately, and severely ill individuals at three timepoints. The first timepoint was at 3 months after the onset of SARS-CoV-2 infection, as confirmed by the Real-Time PCR test, and next timepoints were at 6 and 9 months post infection.

These results indicate that the concentrations of the IgG anti-SARS-CoV-2 antibodies between the groups with mild to moderate disease course, and severe disease did not differ statistically significantly at any of the study's three timepoints.

Comparison of the presence of the IgG anti-SARS-CoV-2 antibodies in relation to sex of the patients

A comparison of the concentrations of the IgG anti-SARS-CoV-2 antibodies depending on the sex of the subjects found that the mean concentrations of the IgG antibodies were very similar between both sexes and amounted to 743.6 IU/mL (Q1-255.6 – Q3-998.2) and 743.4 IU/mL, respectively (Q1-253.5 – Q3-1005.9). Table 2 presents the differences and changes in the concentrations of the IgG anti-SARS-CoV-2 antibodies between females and males at three-time points – at 3, 6, and 9 months post infection with SARS-CoV-2.

A statistically significant increase in the level of the IgG anti-SARS-CoV-2 antibodies was found at 3 months post infection both in males – 1,239.6 IU/mL ($p < 0.001$) and in females – 1,288.5 IU/mL ($p = 0.005$). At 6 and 9 months post infection, the median concentration of IgG antibodies remained at a high level both in males and in females. At month 6 of the study, the concentration of antibodies in females was 1,222.6 IU/mL ($p < 0.001$), and in males – 1,222.4 ($p = 0.002$). At month 9 of the study, the concentration of antibodies in females was 1,385.9 IU/mL ($p = 0.027$) and in males – 1,086.0 ($p = 0.034$). Concentrations of the IgG anti-SARS-CoV-2 antibodies in males and females were not statistically significant at any of the study's three timepoints.

Table 1. Comparison of the presence of anti-SARS-CoV-2 antibodies in the IgG class between the groups of individuals with mild or moderate, and severe courses of the disease

Timepoint ¹		Group I Severe course of the disease	Group II Mild or moderate course of the disease	P
3	N Median concentration (25%, 75%)	18 1,371.1 ² (740.1; 1508.1)	138 1,196.0 ² (725.9; 1470.4)	0.391
6	N Median concentration (25%, 75%)	5 1,137.3 ² (1082.1; 1649.1)	91 1,225.5 ² (663.8; 1445.0)	0.542
9	N Median concentration (25%, 75%)	3 1,435.2 ² (1402.9; 1557.4)	66 1,265.1 ² (856.9; 1631.8)	0.453

¹ Months; ² IU/mL

Table 2. Comparison of the presence of anti-SARS-CoV-2 antibodies in the IgG class in individuals depending on their sex

Timepoint ¹		Males	Females	P
3	N Median concentrations (25%, 75%)	99 1,239.6 ² (720.2; 1510.9)	57 1,288.5 ² (746.6; 1450.1)	0.938
6	N Median concentrations (25%, 75%)	66 1,222.6 ² (728.1; 1480.8)	30 1,222.4 ² (725.1; 1395.5)	0.816
9	N Median concentrations (25%, 75%)	46 1,385.9 ² (972.9; 1667.7)	23 1,086.0 ² (833.1; 1561.7)	0.302

¹ Months; ² IU/mL

Discussion

Our study shows that for individuals with a severe course of the disease the average concentration of the IgG class antibodies was slightly higher than in the group of individuals with a mild disease course. This difference was the highest at 9 months post infection, but it was only 170.1 IU/mL. The study findings suggest that humoral response developing as a result of infection depends on the severity of the condition. However, the conducted analysis does not show whether a high titre of the IgG class antibodies guarantees protection against subsequent infections. Studies conducted on macaques, as well as epidemiological studies into Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) infections, show that the presence of the IgG class anti-SARS-CoV-2 antibodies protects individuals from re-infection with SARS-CoV-2 [18–20].

The analysis conducted in this study, involving 18 individuals with a severe course and 138 individuals with a mild course of the disease, does not allow us to draw such far-reaching conclusions, as the period of observation of the convalescents was too short. Other researchers studying the efficacy of serological tests to assess the risk of re-infection, also believe that the presence of IgG antibodies may not be consistent with long-term immunity [18].

The results of the present study allow for the conclusion that individuals with a severe course of COVID-19 have slightly higher concentrations of immunoglobulins than individuals with a mild course. Similar conclusions were reached by scientists who analysed the concentration of IgG anti-SARS-CoV-2 antibodies [1]. They showed that virus-specific antibody titres were elevated in individuals with severe COVID-19 in comparison to asymptomatic individuals or those with a mild course of the disease [1].

These reports raise concerns about the effectiveness of humoral response in the course of infection and its evaluation as an indicator of groups at risk of re-infection. Another large retrospective study, which examined 38 serological tests, analysing IgG and IgM levels, indicated the validity of conducting serological tests only to differentiate between active and past infection with SARS-CoV-2 [21]. The suggestion that the quality rather than the quantity of antibodies may predict the outcome of infection was made in a recent report that used a panel of serological tests in 22 individuals with COVID-19 [10]. The titre of antibodies was higher in 10 individuals who died as a result of the infection than in 12 convalescents [10].

The study showed that the individuals who suffered a fatal outcome of the disease had an increased percentage of antibodies that stimulate phagocytes and neutrophils and a decreased level of antibodies that activate natural killer cells and recruit the complement [10]. The convalescents, on the other hand, had an increased concentration of antibodies stimulating natural killer cells and the complement system [10]. This study also showed that the survivors had higher titres of S-specific IgM and IgA1 antibodies against SARS-CoV-2, while in fatal cases an increase in titres of IgM and IgA1 antibodies targeting the N protein of the virus was observed [10].

It should be taken into consideration that humoral response is not the only mechanism contributing to the acquisition of long-term immunity in the event of COVID-19 infection. An enhanced T-cell response is described for most SARS-CoV-2 infections as the body's primary response to ongoing infection [22–24]. Melgaco et al., in their *in vitro* model, showed that infection of Peripheral Blood Mononuclear Cells (PBMC cells) with SARS-CoV-2 activated CD4+ memory cells that guarantee immunity [25]. Scientists point out that T cells play the main role in achieving immunity to infection with SARS-CoV-2. Therefore, analysing exclusively the parameters of humoral immunity in the assessment of re-infection is an inappropriate and unjustified approach. Other researchers found that members of the Bcl-2 family had modulated in the T cells of COVID-19 patients. More importantly, they demonstrated that the pan-caspase inhibitor, Q-VD, prevented T cell death by apoptosis and enhanced Th1 transcripts. Altogether, these results are compatible with a model in which T-cell apoptosis accounts for T lymphopaenia in individuals with severe COVID-19. Therefore, a strategy aimed at blocking caspase activation could be beneficial for preventing immunodeficiency in COVID-19 patients [26].

Our study did not show any significant differences in IgG anti-SARS-CoV-2 antibody concentrations between the sexes. It was shown that in both males and females, the median IgG antibody concentration was very similar – 743.6 IU/mL and 743.4 IU/mL, respectively. Both males and females showed a significant increase in IgG anti-SARS-CoV-2 antibodies during the 9-month observation period, but no significant differences were observed between the sexes. Similar results were obtained by Ishaq SE et al. who analysed the concentrations of IgG and IgM anti-SARS-Cov-2 antibodies in 383 males and 344 females [27]. The results showed that there was no significant difference in the production of both IgM and IgG in males in comparison to females [27]. The study of

489 convalescents did not show any differences between the IgG and IgM class anti-SARS-CoV-2 antibodies in males compared to females [28]. On the other hand, numerous studies of seroconversion of anti-SARS-CoV-2 antibodies indicate that age significantly affects the production of IgG antibodies [28–30]. In our study, significant differences based on age were observed at 3 months post infection. In the group of individuals over 60 years old, the concentration of the antibodies was 860.2 IU/mL and it was much lower than in the individuals at the age below 60, where the level of the antibodies was found to be 1,362.4 IU/mL. At 6 and 9 months post infection, the concentrations of the antibodies remained at a high level, and was comparable in both groups. The results of the present study are consistent with the current theory that the immune system of the elderly is less efficient, which is why the elderly are at a higher risk of severe course of infections. As regards the aging process, Andre et al. showed that COVID-19-infected patients presented with lymphopaenia, which was reported as being related to abnormal programmed cell death. Their findings demonstrated that individuals with high levels of CD4 T-cell apoptosis and CXCL10 have a poor ability to build an efficient anti-S response. Detailed T cell responses could be developed as their S-transfected cells (S-Flow) assays and CXCL10 concentration measurement provide a helpful indication [31].

Another aim of our study was to assess the effectiveness of vaccines in the synthesis of IgG SARS-CoV-2 specific antibodies. Korang, Hall, Baden, et al. proved in their publications that the two mRNA vaccines available on the market – Pfizer/BioNTech, Moderna, and the two vector vaccines – AstraZeneca and Johnson & Johnson – reduced the risk of the severe course of COVID-19 and the number of hospitalisations as well as morbidity associated with the disease [32–34]. The relationship between the presence of IgG antibodies and a significantly reduced risk of SARS-CoV-2 re-infection has also been documented [35]. The antibodies produced as a result of viral infection or vaccination can improve humoral response and provide protection against re-infection, which can even last for life [36]. Our study demonstrates the effectiveness of vaccines in the development of the humoral immunity in individuals after SARS-CoV-2 infection. In both study groups, at study point 0, there were comparable antibody levels in both vaccinated and unvaccinated individuals: 650.7 AU/mL and 747.9 AU/mL, respectively. At 3 months post infection, there was a rapid increase in the concentration of antibodies in the group of vaccinated individuals, up to 1,373.7 AU/mL. In the unvaccinated group, the antibody concentration was 830.8 AU/mL. The IgG antibody level in the vaccinated group remained at 1,291.5 AU/mL at 6 months post infection, while in the unvaccinated group, the antibody concentration decreased rapidly to 298.1 AU/mL. Nine months after the onset of the infection, the level of IgG antibodies in the group of vaccinated individuals was 1,430.9 AU/mL, while in the unvaccinated individuals it was 661.3 AU/mL. The mean antibody level difference between the vaccinated and unvaccinated subjects was 769.6 AU/mL at the final stage of the study. The evaluation showed that the vaccines were not only associated with faster immunity acquisition, but they were also responsible for maintaining higher concentrations of IgG antibodies for a longer

period of time. The results obtained in the present study are consistent with the findings published by other researchers and confirm the effectiveness of vaccines in antibody production. In a study by Earle et al., a strong correlation was observed between the titre of neutralising antibodies and the titre of IgG antibodies against the Spike protein and the effectiveness of the vaccine despite geographically diverse study populations [37]. Garcia-Beltran et al., in a study of 239 vaccinated individuals, showed the effect of the vaccine, in particular the booster dose, on enhancing the cross-reactivity of the neutralising antibody response [38]. Another published study, involving 33 healthy adult participants, found that after receiving the second dose of the vaccine, high levels of binding and neutralising IgG antibodies were present for 180 days post vaccination, providing effective protection against re-infection with SARS-CoV-2 [39].

The study showed that taking the vaccine significantly affected the production of anti-SARS-CoV-2 IgG antibodies in virtually every analysed group. The analysis of the results also revealed that in severely and moderately ill people, vaccinations additionally stimulated humoral response, despite their immunodeficiency and poor overall condition. These analyses validate the effectiveness of vaccinations in preventing the severe course of COVID-19 and also show that even in patients who have recovered from the infection, the vaccines enhance the production of IgG antibodies and facilitate the development of secondary immune response.

The findings also suggest that people who were severely and moderately ill with COVID-19 showed a greater motivation to vaccinate compared to people with mild symptoms. In severely and moderately ill patients, at 6 and 9 months post infection, the number of vaccinated patients was 78% and 85%, respectively. Unfortunately, this shows that the main factor encouraging people to get vaccinated is the severity of infection.

However, studies analysing the concentration of IgG antibodies in convalescents and patients recovering from COVID-19, who were given the mRNA vaccine, showed that hybrid immunity resulted in a better antibody response, and people who had no previous infection would need a booster dose earlier than infected individuals [11]. We observed a rapid decrease in antibody titre in the group of unvaccinated individuals at month 6 of the follow-up, from 830.8 AU/mL (month 3) to 298.1 AU/mL. Such results have not yet been reported in the available literature. This fact can be explained by the effects of immunosuppressive treatment in this study group. Undoubtedly, there is a need for further observational studies to thoroughly understand all the mechanisms of acquiring immunity after SARS-CoV-2 infection. On the basis of the results of the present study and the data in the available literature, it cannot be concluded whether anti-SARS-CoV-2 antibodies created post-vaccination are a reliable indicator of the effectiveness of preventive vaccinations. Undoubtedly, in the development of long-term immunity, the mechanisms of cellular immunity should also be taken into account. It is also necessary to conduct further population studies in the long term to be able to assess the effectiveness of vaccinations.

Conclusions

The concentration of IgG anti-SARS-CoV-2 antibodies in the group of patients with severe signs of SARS-CoV-2 infection is significantly higher in comparison to the group of individuals with mild and moderate course of the disease. However, the analysis of antibody concentration did not allow us to draw any conclusions about the severity of the course of the disease. The level of IgG class anti-SARS-CoV-2 antibodies is not a parameter which is dependent on the sex of affected individuals, but rather on their age. In individuals over the age of 60 years old, the production of IgG anti-SARS-CoV-2 antibodies is lower. In vaccinated individuals in this age group, the level of IgG anti-SARS-CoV-2 antibodies is higher than in unvaccinated individuals, however, the assessment of the titre of IgG anti-SARS-CoV-2 antibodies alone should not be a determinant of the validity of vaccination.

The assessment of the titre of the IgG anti-SARS-CoV-2 antibodies is not a parameter determining the effectiveness of the vaccination but rather an indicator of past infection. Also, this parameter is insufficient for the assessment of the risk of re-infection, as well as the effectiveness of vaccination.

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EPISTAXIS AS A SERIOUS COMPLICATION OF HIGH FLOW NASAL CANNULA

Krwotok z nosa jako poważne powikłanie wysokoprzepływowej tlenoterapii donosowej



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Abstract

Introduction: High flow nasal cannula is a commonly known therapeutic option for acute respiratory failure in COVID-19 and other lung disorders. Together with non-invasive ventilation, it is a bridging therapy before invasive respiratory support, and often allows to avoid the latter. High flow nasal cannula has a favourable safety profile. However, the purpose of this case report is to draw attention to a rare yet potentially fatal complication of this therapeutic method. **Case report:** The paper describes a 63-year-old Caucasian male admitted to the Department of Infectious Diseases in April 2021 due to the critically severe course of COVID-19 with 90% lung tissue involvement as shown on computed tomography scans. From the beginning, the patient underwent high flow nasal cannula therapy. After 3 days of treatment, he developed massive nasal haemorrhage. Despite an immediate anterior nasal packing, the epistaxis led to rapid respiratory deterioration, which necessitated intubation and invasive ventilation. Cardiac arrest with pulseless electrical activity occurred in spite of measures taken. **Discussion:** The patient died after unsuccessful resuscitation. The risk of epistaxis, which may result in a critical deterioration of patient's respiratory capacity, must be taken into account when high flow nasal cannula is implemented. **Conclusions:** In view of increasing popularity of the discussed therapeutic method, there is an urgent need for cohort studies in order to assess risk factors and proper preventive measures in epistaxis resulting from the use of high flow nasal cannula.

Streszczenie

Wstęp: Wysokoprzepływowa tlenoterapia donosowa jest obecnie powszechnie stosowaną metodą leczenia ostrej niewydolności oddechowej w przebiegu COVID-19 i innych chorób płuc. Wraz z nieinwazyjną wentylacją mechaniczną stanowi ona leczenie pomostowe przed wdrożeniem respiratoroterapii inwazyjnej, częstokroć pozwalając na jej uniknięcie. Wysokoprzepływowa tlenoterapia donosowa cechuje się korzystnym profilem bezpieczeństwa. Prezentacja niniejszego przypadku ma jednak na celu zwrócenie uwagi na rzadkie, ale potencjalnie śmiertelne powikłanie tej metody terapeutycznej. **Opis przypadku:** W pracy przedstawiono opis przypadku 63-letniego mężczyzny rasy białej hospitalizowanego w oddziale chorób infekcyjnych w kwietniu 2021 roku z powodu krytycznie ciężkiego przebiegu COVID-19 z zajęciem 90% tkanki płuc w obrazach tomografii komputerowej. Od początku pobytu w Klinice u chorego stosowano wysokoprzepływową tlenoterapię donosową. Po trzech dniach leczenia doszło u niego do masywnego krwotoku z jamy nosa, który pomimo niezwłocznego założenia tamponady przedniej doprowadził do gwałtownej dekompensacji oddechowej wymagającej intubacji i włączenia respiratoroterapii. Mimo podjętych działań doszło do zatrzymania krążenia w mechanizmie czynności elektrycznej bez tętna. **Omówienie:** Po nieskutecznej resuscytacji pacjent zmarł. Podczas stosowania wysokoprzepływowej tlenoterapii donosowej należy zatem uwzględnić ryzyko wystąpienia krwotoku z jamy nosa, mogącego skutkować krytycznym pogorszeniem wydolności oddechowej. **Wnioski:** Z uwagi na rosnącą popularność omawianej metody terapeutycznej konieczne są badania kohortowe mające na celu ocenę czynników ryzyka wystąpienia krwotoku z nosa, a także sposobów zapobiegania temu poważnemu powikłaniu.

Keywords: epistaxis; pneumonia; COVID-19; nasal cannula

Słowa kluczowe: krwawienie z nosa; zapalenie płuc; COVID-19; tlenoterapia donosowa

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Introduction

The COVID-19 pandemic has given rise to a huge demand for techniques utilised in the treatment of acute respiratory failure, including mechanical ventilation. The limited capacity of healthcare systems in terms of ventilator sites and the unsatisfactory outcomes of this therapeutic approach have forced the search for new bridging therapies. The goal in this case is to postpone (or ideally avoid) the need for invasive ventilator therapy with all its known complications for as long as possible. The pandemic situation has given rise to the widespread use of non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC). Although the latter technique was a particular novelty in the Polish healthcare system, its relatively easy use encouraged its utilisation even under pandemic conditions. HFNC allows for an intranasal delivery of a gas mixture heated to body temperature with FiO_2 up to 1.0 and humidity up to 100%. Depending on the manufacturer, the maximum flow rate ranges from 60 to 80 L/min. The mechanism of this therapeutic method consists in: 1) reducing dead space in the upper airways; 2) increasing the dynamic pressure in the airways; 3) reducing the metabolic cost of breathing and improving mucociliary clearance; 4) preventing bronchial obstruction in response to cold. The first two effects depend on the set flow rate, while the third and fourth result from the optimal physicochemical parameters of the respiratory mixture [1, 2].

In pre-pandemic times, hypoxemic respiratory failure was the main indication for HFNC. Although this method can be also used in hypercapnic respiratory failure, it is advisable to first attempt NIV in such cases, as in line with the current recommendations of the European Respiratory Society (ERS) [3].

HFNC is also recommended in patients:

- after extubation (postoperative in particular);
- as part of oxygenation before intubation;
- during NIV intervals;
- in the treatment of acute heart failure;
- in perioperative oxygen therapy during bronchofiberoscopy.

Treatment of severe respiratory failure in patients with contraindications to mechanical ventilation (do not intubate, DNI) is an important indication, the role of which has significantly increased during the COVID-19 pandemic [4].

Complications of HFNC, such as barotrauma, gastric distension, aspiration of secretions, or epistaxis, seem to be relatively rare in both adults and children. So far, they have not been considered a significant therapeutic problem; however, some cases had been reported even before the COVID-19 pandemic [5]. The literature estimates that 0.6–10% of patients develop epistaxis during HFNC therapy; however, the authors emphasise that these were retrospective case studies without randomisation [6, 7]. These reports concerned patients treated in intensive care units (ICUs) for reasons other than COVID-19.

This paper presents a case of a 63-year-old man hospitalised in the Department of Infectious Diseases in April 2021 due to a critically severe course of COVID-19, with

90% lung tissue involvement in computed tomography (CT). The patient was treated with HFNC due to acute hypoxemic respiratory failure, and developed severe nasal bleeding during treatment.

Case report

A 63-year-old man was admitted to the Department of Infectious Diseases as an emergency due to respiratory failure and pneumonia in the course of COVID-19. The patient was on chronic treatment for hypertension and type 2 diabetes mellitus (T2DM). He received amlodipine 10 mg/day, indapamide 1.5 mg/day, telmisartan 80 mg/day and metformin 1000 mg/day. He also reported a history of an episode of atrial fibrillation years ago, but he was not on anticoagulation, and he had no documentation to confirm arrhythmia. He denied chronic upper respiratory tract diseases and laryngological interventions. He did not report epistaxis in the past. On taking medical history, the patient complained of severe general weakness and muscle pain from a week before admission. Therefore, an outpatient antigen test for SARS-CoV-2 was performed, which was inconclusive. Also, he had developed dyspnoea two days before admission. Epidemiological history revealed exposure to a person infected with SARS-CoV-2 at work.

On the day of admission, the emergency medical service called by the patient found severe respiratory failure, with 67% saturation while breathing atmospheric air. After applying an oxygen mask with a reservoir bag, with an oxygen flow of 15 L/min, saturation increased only to 91%. During diagnosis at the Hospital Emergency Department, chest CT showed massive interstitial densities manifesting as ground-glass opacification in both lungs, with thickening of the interlobular septa, minor parenchymal consolidations and band-like densities, including subpleural bands, as well as bronchiectasis – COVID-19 CT score of 23/25 and CO-RADS 5. Additionally, a subpleural nodule of 7 × 6 mm in size, an enlarged heart, a hypodense focus of 6 × 3 mm in the left thyroid lobe, as well as a hiatal hernia of the diaphragm and signs of fatty liver were described (fig. 1).

The patient was in serious condition on admission to the ward. Physical examination revealed signs of respiratory failure and obesity (body weight about 115 kg and height 180 cm). Electrocardiogram showed regular sinus rhythm. Laboratory tests revealed significantly elevated C-reactive protein (CRP) and ferritin, neutrophilia with lymphopenia, hyperglycaemia, mild hyponatremia and a moderately increased transaminase activity. IL-6 was also elevated (297.6 pg/mL; reference range 0–150 pg/mL). The coagulation profile did not show any significant abnormalities during hospital stay, with aPTT of 27.5 s (reference range 23–35 s), Quick index of 88% (reference range 80–120%), and D-dimers of 0.6 µg/mL (reference range 0–0.5 µg/mL). Genetic testing with reverse transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection.

Antiviral therapy with remdesivir at a dose given in the SmPC, parenteral broad-spectrum antibiotic therapy with ceftriaxone at a dose of 2000 mg/day with clarithromycin 1000 mg/day, as well as enoxaparin at an interme-

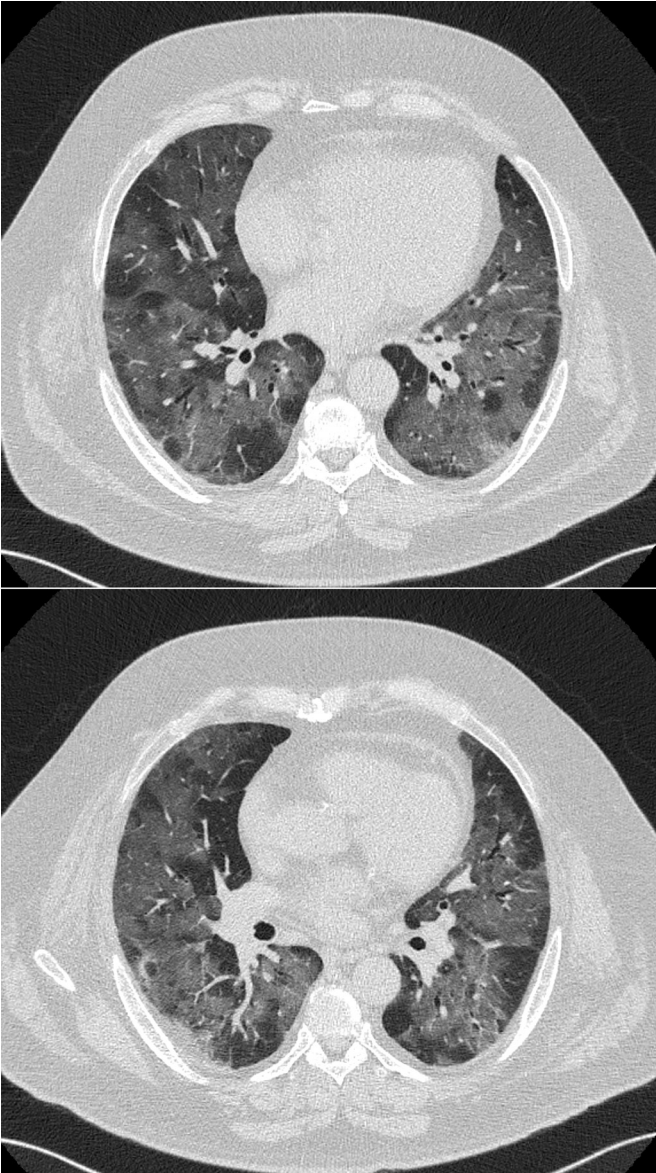


Figure 1. Massive interstitial ground glass opacities, with thickened interlobular septa and small peripheral parenchymal consolidations

diate dose of 60 mg/day, anti-inflammatory dexamethasone 8 mg/day, and fluid therapy were started. Two units of convalescent plasma were transfused. Insulin therapy, as well as medications that the patient was taking regularly, except for metformin, were included.

The patient was undergoing oxygen therapy on admission, with a flow of 15 L/min using a face mask with a reservoir bag. Despite these measures, desaturation below 90% occurred. Due to the increasing hypoxemic respiratory failure, it was considered advisable to initiate HFNC. Nasal oxygen cannulas (NAC) were fitted to the patient's anatomy (1 L, size L; fig. 2) and the therapy was implemented using the Respirecare Hifent HUMID-BH system (Shenyang RMS Maisi Medical Technology Co., Ltd., China), with flows of 60–80 L/min, f_{iO_2} approx. 0.95 and a temperature of the gas mixture of 37°C (fig. 3).

On day 4 of hospital stay, in the evening, the patient developed massive nasal haemorrhage, which was ini-



Figure 2. Nasal cannulas of various sizes used during high-flow nasal cannula therapy

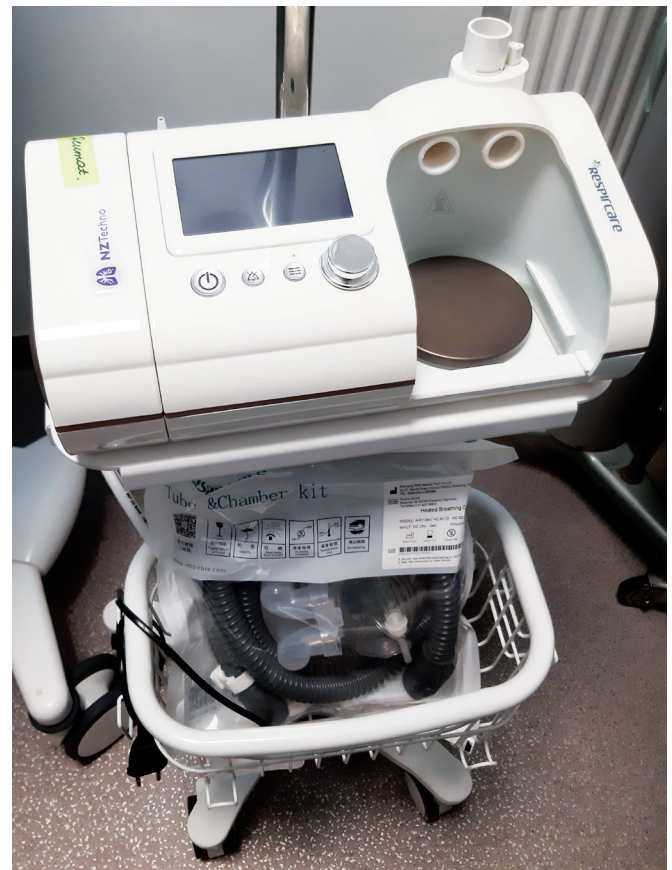


Figure 3. System for high-flow nasal cannula therapy

tially controlled locally with intranasal packing with epinephrine and etamsylate, prepared *ex tempore*, using Adrenalina WZF 0.1% (Polfa Warszawa SA, Poland) and Cyclonamine 12.5% (FSP "Galena", Poland), respectively. However, the subsequent deterioration of the patient's respiratory function and desaturation of up to 85% in pulse oximetry indicated that HFNC was considered insufficient. A bridging attempt was made to apply continuous positive airway pressure (CPAP) using the Trilogy Evo device (Philips, USA) and a full-face mask with $f_{iO_2} = 1.0$ and positive end expiratory pressure (PEEP) of 10 cm H₂O. Satisfactory saturation values of 91–92% were achieved, but the patient reported mask intolerance. Additionally, the patient's blowing of cold compresses and clots from the nasal cavities led to bleeding recurrence. An otorhinolaryngologist was called in and applied an anterior nasal packing to both nasal cavities, which effectively controlled the bleeding. However, he was unable to determine the site of bleeding due to the rapidly deteriorating condition of the patient.

At the same time, due to the exhaustion of non-invasive treatment options for respiratory failure, an anaesthesiologist was called in to intubate the patient and initiate mechanical ventilation (Puritan Bennett, USA). Despite the suction of blood clots from the respiratory tract and optimisation of the ventilator settings, hypoxia rapidly increased, with electrocardiography showing increasing Pardee waves as a manifestation of type 2 myocardial infarction. Soon, a sudden cardiac arrest occurred in the mechanism of pulseless electrical activity (PEA). Resuscitation was initiated in accordance with the current protocol of the Polish Resuscitation Council [8]. Despite measures taken, the rhythm went into permanent asystole and finally, after unsuccessful resuscitation, the patient was pronounced dead.

Discussion

Patients with SARS-CoV-2 infection are a specific group frequently presenting with coagulopathy. Although it usually manifests with higher rates of thromboembolic events, an increased tendency to haemorrhages, including epistaxis, has also been described [9–12]. The aetiology may be both systemic and local. The first group includes the use of coagulation factors and the impact of anticoagulant therapy, i.e. low-molecular-weight heparins, routinely used in COVID-19. This has been confirmed in a case series by Dell'Era et al. [13]. The authors emphasise that prolonged oxygenation with a nasal cannula contributes to increased nasal dryness and is a risk factor for crusting, which weakens the nasal mucosa, exposing patients to nasal haemorrhages.

Interestingly, the coagulation profile did not show any significant deviations from the norm in the discussed case. However, given the anticoagulant treatment with low-molecular-weight heparin used during hospital stay, it is difficult not to consider its potential impact on the occurrence of bleeding. In turn, the inflammation of the nasal mucosa associated with a viral infection, which also seems to be the cause of damage to the olfactory nerve endings and anosmia, may have been a local factor in this case [14, 15]. Therefore, even in the absence of obvious

rhinological problems, there may be a tendency to bleed from the submucosal plexuses.

It therefore seems that both systemic and local factors played an important role in the presented case. Their overlap had a dramatic effect on the patient, as the bleeding into the upper respiratory tract irreversibly deteriorated arterial blood oxygenation. It is worth noting that the patient's respiratory reserve was critically low due to 90% lung involvement.

Current international guidelines for the management of sepsis recommend the use of NIV or HFNC in patients with severe hypoxia requiring non-invasive oxygen therapy to avoid complications of intubation. The authors emphasise that self-limiting complications associated with HFNC are possible, but usually do not require treatment discontinuation [16].

Although there are no absolute contraindications to HFNC, its use should be carefully considered in patients with impaired consciousness, as measured with the Glasgow Coma Scale, reduced upper airway reflexes, claustrophobia, risk of aspiration, unstable hemodynamics or epistaxis [1, 2]. However, in the case discussed, it was the HFNC therapy itself, overlapping with the above-mentioned coexisting local and systemic factors, that may have contributed to the bleeding.

Conclusions

When using HFNC, the risk of epistaxis should be taken into account as it may lead to a critical deterioration of respiratory function in the patient. Due to the growing popularity of this treatment approach, cohort studies are needed to assess the risk factors for epistaxis, as well as methods to prevent this serious complication.

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RHINOPHYMA – SURGICAL EFFICACY

Rhinophyma – skuteczność leczenia chirurgicznego



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Abstract

Rhinophyma is a rare form of rosacea leading to nasal deformation and deterioration in the patient's quality of life. This article presents a clinical case of a 70-year-old patient with advanced rhinophyma, who presented with nasal redness, thickening, and deformation, significantly affecting his social and psychological functioning. After a thorough clinical assessment, surgical removal of the excessively thickened nasal tissue was decided upon. Following the surgery, the patient achieved significant improvement in facial aesthetics and experienced a reduction in respiratory symptoms. Surgical treatment of rhinophyma can be an effective therapeutic method in cases of advanced nasal changes, contributing to an improvement in the quality of life and satisfaction with appearance.

Streszczenie

Rhinophyma jest rzadką formą trądziku różowatego, prowadzącą do deformacji nosa i pogorszenia jakości życia. W artykule przedstawiono przypadek kliniczny 70-letniego pacjenta z zaawansowaną guzowatością, który zgłosił się z zaczerwienieniem, zgrubieniem i deformacją nosa, które znacznie wpływały na jego funkcjonowanie społeczne i psychologiczne. Po wnikliwej ocenie klinicznej zdecydowano się na chirurgiczne usunięcie nadmiernie zgrubiałej tkanki. Po operacji pacjent osiągnął znaczną poprawę estetyki twarzoczaszki oraz redukcję objawów ze strony układu oddechowego. Leczenie chirurgiczne *rhinophyma* może być skuteczną metodą terapeutyczną w przypadkach zaawansowanych zmian nosa, przyczyniającą się do poprawy jakości życia i zadowolenia z wyglądu.

Keywords: rosacea; reconstructive surgery; rhinophyma

Słowa kluczowe: trądzik różowaty; chirurgia rekonstrukcyjna; *rhinophyma*

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Introduction

Rhinophyma, or nasal tuberosity, is a variant of rosacea characterised by abnormal growth of nasal tissue and progressive hypertrophy. The disease manifests with proliferation of sebaceous glands, connective tissue and blood vessels, leading to nasal thickening and deformity [1]. In the early stages of the disease, redness and a few small nodules appear on the nose. Over time, the nose becomes increasingly enlarged and bulbous. The affected skin is stretched, with prominent pores and scars. This results in nasal deformation and, consequently, physical and mental discomfort for patients.

Rhinophyma typically affects middle-aged to elderly men, mainly Caucasian [2]. Its aetiology ranges from aggravation of rosacea to intracellular oedema of the skin due to immune-mediated vasodilatation. There is also empirical evidence to support increased hypertrophy following alcohol or caffeine consumption and in the presence of the skin mite *Demodex folliculorum* [3]. The diagnosis is based primarily on clinical examination, with diagnostic confirmation of collected specimens by histology. Microscopic examination shows thickening of the dermis and epidermis and hypertrophy of the sebaceous glands. An associated inflammatory infiltration, consisting of lymphocytes, plasma cells and Lang-

hans-type multinucleated giant cells, is also observed. A thorough histopathological diagnosis is necessary to confirm or exclude basal cell carcinoma (BCC), which is found in 3–10% of rhinophyma cases [4].

Surgery is the most effective treatment for advanced nasal tuberosity. Among the many invasive techniques available, it is worth mentioning the classical surgical methods, such as reducing or removing nodules with a scalpel, with simultaneous wound coverage with a free skin flap or a split-thickness skin graft.

This paper presents a case report of a patient with rhinophyma who underwent surgical intervention to improve nasal aesthetics and quality of life.

Case report

A 70-year-old man presented to the Department of Plastic and Reconstructive Surgery and Burns Treatment with prominent symptoms of rhinophyma, which were significantly affecting his psychological and social well-being and causing difficulty in breathing through nose (fig. 1). After a thorough clinical examination and assessment of the patient's condition, a decision was made to perform a surgery to remove the excess nasal tissue. Preoperatively, the skin area was locally anaesthetised with a 1% lidocaine solution.

The procedure started with the removal of the nodules on the dorsum of the nose, with a depth of excision of approximately 1 mm. Analogous procedures were then performed on the nasal alae. The key element was to remove the layers precisely and symmetrically in order to ultimately achieve the desired shape of the nose and to prevent cartilage exposure on the dorsum and iatrogenic perforation of the nasal cavity. Blood vessels were closed by electrocoagulation and intraoperative specimens were sent to the laboratory for histopathological examination. After complete removal of all layers of deformity and restoring nasal symmetry, an intermediate-thickness skin graft (0.3 mm), which was collected intraoperatively from the anterior surface of the thigh using a dermatome, was applied (fig. 2). The first postoperative follow-up (2 days after surgery) showed a reduction in nasal size and redness (fig. 3). One week later, during another follow-up visit, the sutures were removed, confirming normal wound healing and graft acceptance. One month after surgery, the operated area was found to be completely healed, with no visible postoperative marks, and the natural shape of the nose was restored.

Postoperatively, the patient quickly regained full activity. After a few weeks, there was a marked improvement in nasal aesthetics and increased patient satisfaction with the treatment outcomes.

Discussion

Various therapeutic approaches may be used for nasal tuberosity. However, despite further development of the available technologies, there is still no consensus on which technique is most optimal. Oral isotretinoin has been shown to be effective in reducing nasal redness and sebaceous gland hypertrophy. CO₂ and Nd:YAG lasers



Figure 1. Patient directly before surgery



Figure 2. Patient directly after surgery



Figure 3. Postoperative control 2 days after surgery

are a commonly chosen strategy for thickened nasal skin as the laser beam effectively reduces nodules and thickenings [5]. Dermabrasion, i.e., mechanical removal of the upper layers of the skin, is another treatment option. However, it is important to note that this therapy carries the risk of excessive bleeding in the treated area and may lead to scarring. Electrosurgery and electrocautery are also commonly used treatment methods that employ high-frequency electrical current to remove excess nasal tissue.

The Versajet system is one of the latest techniques in the treatment of rhinophyma. This device, which utilises a high-speed stream of sterile saline, allows for controlled tissue excision, while simultaneously sucking up the remains of tissue already excised to maintain a clean surgical field [6].

In the case of our patient, a decision was made to perform surgical treatment due to significant disease progression. Additionally, surgical approach offered the greatest chance for radical treatment of the lesion and allowed for later histopathological diagnosis for the presence of malignancy, which is not always possible with other therapeutic methods.

Surgical management of rhinophyma often yields permanent outcomes, unlike other methods that may require regularly repeated follow-up procedures. Mechanical removal of hypertrophied nasal tissue allows for satisfactory cosmetic outcomes by restoring natural nasal appearance, and minimizes potential complications in the surrounding tissue.

Conclusions

The use of a surgical technique to treat rhinophyma in this particular patient proved effective, yielding the desired aesthetic outcome and improving the quality of life. The split-thickness graft provided a very good cosmetic outcome, satisfactory for both the patient and the surgeon.

It should be emphasised that each patient with rhinophyma requires an individual approach and assessment, with the choice of treatment strategy tailored to the needs and capabilities of the patient. The presented case confirms the efficacy of surgical treatment of rhinophyma and emphasises the importance of an interdisciplinary approach to the diagnosis and treatment of this condition in order to achieve optimal therapeutic outcomes.

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EFFECTS OF OCTREOTIDE PHARMACOTHERAPY IN THE TREATMENT OF COMPLICATED PERFORATION OF RETROPERITONEAL DUODENAL ULCER

Skuteczność farmakoterapii oktreotydem w leczeniu umiejscowionego zaotrzewnowo wrzodu dwunastnicy powikłanego perforacją



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Abstract

Duodenal ulcer is a defect in the mucosa. The main aetiological factors are *H. pylori* infection, nonsteroidal anti-inflammatory drugs, genetic factors, and nicotinism. Statistics confirm that perforation is a significant and potentially life-threatening ulcer complication in the Polish population. Octreotide is a somatostatin derivative that works by inhibiting the release of proteins of the gastrointestinal-pancreatic system. It is indicated in acromegaly, hormonally active gastrointestinal tumours, and oesophageal variceal bleeding. It can be used to reduce bile secretion and slow down gallbladder motility. The material for this review paper was a case of duodenal perforation in a woman aged 63 years. Octreotide used in the treatment of a difficult-to-heal anastomosis improved the patient's local and general condition, and led to the closure of the anastomosis. Despite the significant number of circumstances leading to the patient's life-threatening condition in the course of the perforation, there were also factors that positively influenced the treatment outcome. The most important of these was the use of octreotide to increase the chances of healing of the intestinal-intestinal anastomosis in the area of influence of digestive enzymes. The conclusions drawn from this case suggest that octreotide can be used in the treatment of non-healing, properly performed gastrointestinal anastomoses. More effective prophylaxis, early diagnosis of peptic ulcer disease, and increasing access to endoscopy are known to reduce the number of perforation cases. Importantly, there are cases of perforations that can be life-threatening for the patient even in the course of anastomotic dissections of properly performed surgical procedures. Octreotide should be considered in the management of complicated and extreme perforations. This paper describes the possibility of using octreotide as a pharmacotherapy to increase the chances of gastrointestinal anastomosis healing in cases involving complicated duodenal perforations.

Streszczenie

Wrzód dwunastnicy stanowi miejscowy ubytek w błonie śluzowej pokrywającej wewnątrz tego odcinka przewodu pokarmowego. Do głównych przyczyn choroby wrzodowej dwunastnicy zalicza się zakażenie bakterią *H. pylori*, stosowanie niesteroidowych leków przeciwzapalnych, predyspozycje genetyczne oraz palenie tytoniu. Dane statystyczne wskazują, że w polskiej populacji ciężkim i potencjalnie zagrażającym życiu powikłaniem choroby wrzodowej jest perforacja wrzodu. Oktreotydem jest pochodną somatostatyny. Działa poprzez hamowanie uwalniania peptydów wytwarzanych przez wewnętrzny układ żołądkowo-jelitowo-trzustkowy. Lek ten jest wykorzystywany w terapii akromegalii, hormonalnie czynnych guzów przewodu pokarmowego oraz krwawień z żyłaków przełyku. Może być również stosowany w celu zmniejszenia wydzielania żółci i spowolnienia motoryki pęcherzyka żółciowego. Punktem wyjścia dla poniższej pracy przeglądowej był przypadek perforacji wrzodu dwunastnicy u 63-letniej pacjentki. W leczeniu trudno gojącego się zespolecia zastosowano oktreotydem. Lek ten poprawił stan miejscowy i ogólny pacjentki, a także przyczynił się do zamknięcia zespolecia. Pomimo szeregu czynników, które doprowadziły do stanu zagrożenia życia w przebiegu perforacji, odnotowano także okoliczności o korzystnym wpływie na końcowy wynik leczenia. Najważniejszym czynnikiem okazało się wdrożenie leczenia oktreotydem, aby zwiększyć szanse na wygojenie zespolecia jelitowo-jelitowego w obszarze oddziaływania enzymów trawiennych. Opisany przypadek wskazuje na zasadność stosowania oktreotydu w leczeniu prawidłowo wykonanych, ale trudno gojących się zespoleń żołądkowo-jelitowych. Wśród czynników, które przyczyniają się do zmniejszenia liczby przypadków perforacji, należy wymienić skuteczną profilaktykę, wczesne wykrywanie choroby wrzodowej oraz dostęp do badań endoskopowych. Należy jednak zaznaczyć, że przypadki perforacji stanowiących zagrożenie dla życia pacjenta mogą wystąpić nawet przy prawidłowo przeprowadzonym zabiegu zespolecia. W leczeniu złożonych, ciężkich perforacji warto rozważyć wdrożenie oktreotydu. W pracy opisano możliwość zastosowania oktreotydu w ramach farmakoterapii zwiększającej szanse na wygojenie zespolecia żołądkowo-jelitowego u pacjentów z perforacją dwunastnicy.

Keywords: ulcer; octreotide; duodenum; perforation

Słowa kluczowe: wrzód; oktreatyd; dwunastnica; perforacja

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Introduction

Both stomach and duodenum ulcers are mucosal defects, penetrating beyond the *muscularis lamina* with inflammatory infiltration and necrosis, limited in nature [1]. The main aetiological factors include *H. pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, certain genetic factors, such as blood type O, or the gene-dependent number of lining cells in the stomach and their sensitivity to gastrin, are known to promote peptic ulcer disease.

Cigarette smoking is an important factor hindering ulcer healing and increasing the incidence of ulcer disease [1]. The prevalence of duodenal ulcer disease is approximately 55 000 in the adult Polish population, with a three-fold predominance in men [1]. One of its main complications, besides haemorrhage and pyloric stenosis, is ulcer perforation. It affects about 2–7% of patients with peptic ulcer disease [2], with the mortality rate varying between 4–40% [3].

Octreotide is a synthetic somatostatin derivative which, while exhibiting similar properties, demonstrates a longer (1.5-hour) half-life in the blood. The action of this drug involves inhibiting the release of serotonin, the growth hormone, and the proteins of the gastroenteropancreatic (GEP) system [4]. Octreotide is often prescribed in acromegaly, in hormonally active gastrointestinal tumours, and in cases of oesophageal variceal bleeding. Unlike other somatostatin analogues, octreotide is administered in pre- and post-operative prophylaxis in patients referred for surgical treatment of pancreatitis. In addition, when used in single doses, it may decrease bile secretion and suppress gallbladder motility. Possible side effects of octreotide treatment may include pain at the administration site, diarrhoea, gallstones or hyperglycaemia. The dosage used for preventing complications after pancreatic surgery is 0.1 mg 3 ×/d for 7 days [5, 6].

Case report

A female patient, I.P., aged 63 years, was admitted to the Department of General Surgery at the Olesno Complex of Health Care Centres (Case Record No. 3432/2022) with suspected perforation of gastric or duodenal ulcer. On 4 September 2022, she presented to the Emergency Department of the Olesno Hospital with epigastric pain that had persisted for several days. In the course of diagnostics, an abdominal CT scan was performed, suggesting stomach or duodenum perforation. On the same day, the patient was referred and admitted to the Department of General Surgery, where L5-S1 spinal discopathy, the

use of NSAID painkillers, type 2 diabetes mellitus, and hypertension in history were found. The patient denied nicotine use. On admission, her general condition was average. The patient reported rather severe pain; the heart rate was steady (100 bpm) and the blood pressure was 85/55 mmHg. On physical examination, there was abdominal pain in the epigastrium and umbilical region, peritoneal symptoms in the epigastrium and mid-abdomen on the right side, and an umbilical hernia. Laboratory tests yielded the following results: CRP 98.45 mg/L, D-dimers >4.00 µg FEU/mL, blood group – 0 RhD positive, GFR 33 mL/min/1.73 m², Troponin T 28.64 ng/L. The patient was urgently scheduled for surgery. Hydration, thromboprophylaxis, and antibiotic therapy with Biofuroxime 3 × 1.5 g/d and Metronidazole 3 × 0.5 g/d were ordered. A laparotomy was carried out, revealing purulent contents in the peritoneal cavity, sampled for bacteriological examination. Some yellow-coloured contents were visualised in the subhepatic area. An inflammatory infiltrate was found, involving the hepatoduodenal and hepatogastric ligaments. After evacuation of the duodenal contents, an oval perforation, about 20 mm in diameter, was observed in the posterior-superior wall of the duodenum. The attempt to close the hole with sutures was abandoned because of its size, the inflammatory infiltration, and altered anatomical relationships. The rather challenging stump of the duodenum was closed by the Nissen method. Drains were positioned around the stump: one was inserted into the epigastrium, while two other were placed in the mid-abdomen. Subsequently, the stomach was resected by the Billroth II method, followed by Braun's enterostomy. A micro-jejunostomy was guided through an incision in the wall of the jejunum for enteral nutrition. In addition, the patient was fitted with a gastric probe and transferred to the Acute Intensive Care Unit (AICU) for further treatment.

There, the patient was diagnosed with acute respiratory failure, hypovolaemic shock, peritonitis, obesity and, upon a detailed examination of her history, with nicotine use. Blood pressure during norepinephrine infusions was 90/40 mmHg and the heart rate was 80/min. Antithrombotic prophylaxis, analgosedation, and symptomatic treatment were continued. On admission to the AICU, the following were noted: hypoalbuminaemia 2.56 g/dL, hypoproteinaemia 4.18 g/dL, and procalcitonin 26.01 ng/mL. The abdominal culture revealed the presence of *C. albicans*. During the patient's stay at the AICU, she was fed parenterally with SmofKabiven, 986 mL/d, Cernevit, 1 amp/d, and Supleven 1 amp/d. The initial empirical antibiotic therapy was changed to Vancomycin, 1 g/d, Amikacin, 1.5 g/d, and Caspofungin, 50 mg/d. On the third postoperative day, the patient was extu-

bated following an improvement in her general condition. The drains were retained throughout the patient's stay at the Unit; serous-purulent contents were removed through the drain inserted into the anastomotic area. After surgical consultation, a 5% glucose solution was ordered for administration through the jejunostomy. It was recommended that the drains be left in place for the risk of wound dehiscence in the sutured duodenum. The treatment was continued until 11 September 2022, when the patient was surgically consulted again. A small amount of bile-coloured contents was found to flow from the duodenal stump drain. Similar contents were aspirated through the probe from the gastric stump. The duodenal stump was found to be leaking, and a conservative treatment was recommended, with extra- and enteral nutrition. Simultaneously, water-electrolyte and acid-base imbalances were corrected, achieving cardiovascular stabilisation. The results of the follow-up examinations, carried out on 11 September 2022, were as follows: hypoalbuminaemia 2.16 g/dL, total protein 4.40 g/dL, CRP 97.82 mg/L, D-dimers 2.97 µg FEU/mL, GFR >60 mL/min/1.73 m², WBC 20,000/µL, RBC 3.33 million/µL, HGB 10.3 g/dL, NtproBNP 965.5 pg/mL, Procalcitonin 1.87 ng/mL. After surgical consultation, it was decided to transfer the patient to the Department of General Surgery on 11 September 2022.

After the patient was transferred to the Department of General Surgery, the conservative management was maintained. The antibiotic therapy, extra- and enteral nutrition, and symptomatic treatment were carried on. The antibiotic therapy and the treatment with Caspofungin were terminated on 12 September 2022. Fluconazole, 20 mg 1×/d iv, was initiated. On 14 September 2022, taking into account the patient's stable condition, she was gradually tilted to the upright position. After the passing of several loose stools on 17 September 2022, the patient was diagnosed for infection with *C. difficile*, but an immunoenzymatic test was negative. The control of the contents, guided by the drains inserted into the duodenal stump area, was continued. The drains systematically discharged bile contents throughout the period of hospitalisation. On 19 September 2022, an intestinal anastomosis leak test was performed with an orally administered contrast agent, confirming a post-operative leakage in the gastrointestinal tract; for that reason, enteral feeding was discontinued. On 21 September 2022, the patient's condition was described as moderate, with the dressing soaked with the contents coming out from the forming fistula. On the subsequent day, there was an episode of blood pressure rise, corrected by the i.v. administration of Tachyben, 12.5 mg. In addition, it was necessary to change the dressings due to profuse exudate. On 23 September 2022, the patient's condition worsened, with an increased leakage of purulent contents from the surgical wound and in the area of the nutrient fistula. The patient was then scheduled for relaparotomy due to a suspected intestinal fistula, and the procedure was performed immediately. During the surgery, multiple intestinal adhesions were released, and the cavity of the subdiaphragmatic abscess on the left side was opened and rinsed. The gastrointestinal anastomosis and the Braun anastomosis were tight, while bile contents were leaking from the duodenal stump. Drains were placed in the subdiaphragmatic abscess cavity, the opening in the duodenal stump,

the stump area, and in the pouch of Douglas. Intraoperative laboratory results were as follows: hypoalbuminaemia 2.88 g/dL, total protein 5.38 g/dL, CRP 188.97 mg/L, GFR >60 mL/min/1.73 m², WBC 4100/µL, RBC 2.75 million/µL, HGB 8.3 g/dL, and Procalcitonin 0.35 ng/mL. After the procedure, the patient was transferred to the AICU for further treatment.

The patient's condition in the AICU was severe for 20 days. At that time, the prognosis was unfavourable, also because of a range of disadvantageous factors including the patient's age, co-morbidities, and perforation size, increasing the total risk of death to above 30% [7].

On 26 September 2022, the patient was operated twice, due to anastomotic failure. On 28 September 2022, after a surgical consultation, the patient underwent lavage and drainage of the peritoneal cavity, and a VAC dressing was applied, due to drainage failure. Another procedure took place on 1 October 2022 for suspected faecal peritonitis. The micro-jejunostomy was removed for leakage at the insertion site; in addition, numerous adhesions were released and a left-sided subdiaphragmatic abscess was removed. A significant degree of biliary infiltration was found in the duodenal stump area. During subsequent laparotomies, carried out on 5 and 7 October 2022, a significant degree of biliary infiltration was identified, and individual additional sutures were used to close anastomotic leaks, together with a new drain placed in the duodenal stump. However, the effects of these procedures were not satisfactory at all.

The leakage of gastrointestinal contents into the peritoneal cavity could not be contained. In addition to the leakage of the duodenal stump, a fistula persisted at the site of the gastrointestinal anastomosis.

The case was consulted remotely with the staff at the Department of Gastrointestinal Surgery, where it was considered as extremely challenging. However, a revision surgery was recommended to create a new gastrointestinal anastomosis. The patient was reoperated to precisely locate the leaks from the gastrointestinal anastomosis and the duodenal stump. Due to limited experience, the initial plan to perform a new anastomosis was abandoned, and a conservative treatment with octreotide was implemented instead. Octreotide was started, as recommended, at a dose of 250 µg in a bolus, followed by 250 µg/hour on the first day, then 3 mg/day for five subsequent days, and then at the dose of 1.5 mg/day. The patient's condition began to improve gradually after octreotide was added. The outflow volumes from the drains were found to be decreasing. On 20 October 2022, the patient was transferred to the Department of General Surgery for treatment continuation. The patient's test results in the follow-up examinations prior to the transfer were as follows: CRP 30.98 mg/L, WBC 6400/µL, RBC 3.03 million/µL, HGB 9.2 g/dL, Procalcitonin 0.15 ng/mL.

During the patient's stay at the Department of General Surgery, the prescribed care regimen was continued according to the established schedule. Vital parameters, wound healing, and drainage were monitored. Since the amount of contents from the drains was gradually de-

creasing, more drains could be removed. Octreotide was administered at a dose of 1.5 g per day until 7 October 2022. The patient's general condition improved successively with each day, and effective oral nutrition was started on 29 October 2022.

The patient was discharged home on 11 November 2022 in good general condition, with recommended follow-up at the General Surgery Outpatient Clinic. The patient was hospitalised for a total of 69 days, during which she was operated on six times.

Discussion

Ulcer perforation in the upper gastrointestinal tract is one of more dramatic and dangerous complications of reckless NSAID use [8]. Prophylactic therapy with proton pump inhibitors is a legitimate means of preventing this complication in chronic NSAID users [9]. While preventive therapy is recommended, a lack of information or non-compliance among some patients can result in serious complications, including life-threatening gastrointestinal perforation. In case of perforation in the course of peptic ulcer disease, the recommended management is surgery by Billroth II subtotal gastrectomy [10]. The procedure was performed in our patient with a subsequent hospitalisation for individual treatment, along with recommended dietary and lifestyle changes [11]. The surgical procedure and pharmacotherapy were in line with the current medical knowledge, but managing leaking anastomoses proved to be a challenging problem. Despite adhering to good medical practice, both in surgery and in post-operative care, the patient's condition seriously deteriorated. The diagnosed inflammation with exacerbating mechanisms (a direct impact and amount of digestive enzymes) was regarded as the main failure factor. Treatment with octreotide was selected, even though the surgical option proposed by staff at the Department of Gastrointestinal Surgery, i.e. 'new' gastrointestinal anastomosis, seemed the most appropriate approach. Nevertheless, the medical team, fearing other failures and risks, decided to administer octreotide, taking into consideration the potential trade-off between a probably lower efficacy of the applied pharmacotherapy and the safety of the patient. The goal of optimal conditions for duodenal healing was thus met. After a 69-day hospitalisation, the patient could be discharged home.

Summing up, the main factors responsible for the patient's life-threatening condition included:

- the use of NSAIDs without proper medical supervision and the lack of prophylaxis with proton pump inhibitors during analgesic therapy,
- nicotineism,
- genetic conditions, including RhD positive blood type 0,
- the size and location of the perforated ulcer.

The factors which led to the successful outcome included:

- proper selection and execution of the surgical technique and provision of post-operative care in line with good medical practice,
- close cooperation of the medical personnel with clinical consultants,
- innovative use of octreotide in line with postprandial syndrome treatment regimens.

Conclusions

- The discussed case suggests that octreotide can be considered for the management of hard-to-heal anastomoses in the gastrointestinal tract especially in the areas impacted by digestive enzymes that may increase inflammatory processes.
- A more effective prophylaxis, an early diagnosis of peptic ulcer disease, and increased access to endoscopy help reduce the incidence of perforation with such a dramatic course. Still, serious complications of perforation do happen, including those that may put the patient at risk of death not only as a result of bleeding, but also in the course of anastomotic dissections of otherwise properly performed surgical procedures.
- One of the key conditions for the successful treatment of gastrointestinal fistulas is proper nutrition and control of the patient's protein and albumin levels throughout the treatment period.
- The course of treatment documented above implies that octreotide can be used with positive results in cases of complicated and extremely difficult perforations.

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CASE REPORT OF TUBERCULOSIS IN A CHILD WITH UNCLEAR VACCINATION HISTORY: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

Przypadek gruźlicy u dziecka z wątpliwą historią szczepienia: wyzwania diagnostyczne i terapeutyczne



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Abstract

Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, which often affects the lungs, but can also invade other organs. Despite the obligation of universal vaccination against tuberculosis, there are still cases of disease, especially in unvaccinated children. This article describes a clinical case of a 17-year-old girl who was admitted to the hospital with symptoms of pulmonary tuberculosis. The girl presented with cough, fever, and weakness. A chest X-ray confirmed characteristic lesions indicative of tuberculosis. Thorough clinical evaluation and laboratory tests confirmed the diagnosis. The patient had a questionable history of tuberculosis vaccination, which posed a risk factor for infection. Treatment with anti-tuberculosis antibiotics was initiated, and after several months, an improvement in the girl's health status was observed. Follow-up examinations showed regression of lung lesions, confirming therapeutic effectiveness. This case underscores the importance of tuberculosis vaccination and the necessity of monitoring unvaccinated children for prompt detection and treatment of the disease.

Streszczenie

Gruźlica jest chorobą zakaźną, wywoływaną przez bakterię *Mycobacterium tuberculosis*. Może dotyczyć każdego narządu, ale najczęstszą postacią jest gruźlica płuc. Pomimo obowiązku powszechnych szczepień przeciwko gruźlicy zdarzają się przypadki zachorowań, zwłaszcza u nieszczepionych dzieci. W niniejszym artykule opisano przypadek 17-letniej pacjentki, która została przyjęta do szpitala z objawami zapalenia płuc. Dziewczynka zgłosiła się z kaszlem, gorączką i osłabieniem. Wykonano badanie radiologiczne klatki piersiowej, które wykazało zmiany charakterystyczne dla gruźlicy płuc. Wnikliwa ocena kliniczna oraz badania dodatkowe potwierdziły rozpoznanie. Pacjentka miała wątpliwą historię szczepienia przeciwko gruźlicy, co stanowiło czynnik ryzyka zachorowania. Rozpoczęto leczenie przeciwprątkowe i po kilku miesiącach obserwowano poprawę stanu jej zdrowia. Badania kontrolne wykazały regresję zmian w płucach, co potwierdziło skuteczność terapii. Przypadek ten podkreśla sens szczepień przeciwko gruźlicy oraz konieczność monitorowania dzieci nieszczepionych w celu szybkiego wykrycia i leczenia choroby.

Keywords: vaccination; tuberculosis; immigrants; *Mycobacterium tuberculosis*

Słowa kluczowe: szczepienia; gruźlica; imigranci; *Mycobacterium tuberculosis*

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Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). Although the lung is the predominant site of TB, other organs may be also involved. TB is a significant health challenge worldwide, especially in developing countries, where access to healthcare is limited. It is estimated that one-third of the world's population is infected with MTB, with 5–10% of those infected eventually developing the disease [1].

Despite advances in diagnosis and treatment, TB remains a diagnostic and therapeutic challenge, particularly in children with uncertain vaccination status. Paediatric patients have a higher risk of developing active TB, especially those infected before the age of 5 years [2]. Consequently, identifying children with latent infection and providing them with preventive treatment are key to controlling and eliminating TB [3].

The diagnosis of TB in children can be particularly challenging due to non-specific symptoms and the difficulty in obtaining microbiological confirmation. The lack of reliable vaccination data makes the diagnostic process even more complicated. When TB is suspected in a child with an uncertain vaccination history, accurate diagnosis and prompt treatment are essential to prevent disease progression and transmission.

In countries with low rates of TB, symptoms are significantly more likely to occur in immigrants than in the resident population. This epidemiological situation persists during the first years of residence in the host country [4]. In fact, the majority of new TB cases in the Western paediatric population occur in children born to immigrant families [5].

In the case presented below, we highlight the importance of a thorough clinical assessment, including a detailed medical history and appropriate diagnostic investigations.

Case report

A 17-year-old female patient of Ukrainian origin was admitted to the Department of Paediatrics, Nephrology and Paediatric Allergology due to epigastric pain occurring for 3 days, episodes of fever up to 38°C, and cough persisting for about a month. The girl had been diagnosed with bronchitis two weeks before. Amoxicillin with clavulanic acid was used for treatment, without significant improvement.

On admission, the patient was in a relatively good general condition. Significant abnormalities included yellowing of the skin, isolated crackles in the middle field of the left lung on auscultation over the lung fields, epigastric pain on palpation and a weakly positive Chelmonski sign.

Laboratory workup revealed moderately elevated inflammatory markers (CRP 3.2 mg/dL; normal <0.5 mg/dL), with high ESR (95 mm), elevated total bilirubin (2.3 mg/dL; normal 0.0–1.2 mg/dL) and conjugated bilirubin (1.0 mg/dL; normal 0.0–0.2 mg/dL), with normal aspartate aminotransferase, alanine aminotransferase,

gamma-glutamyl transpeptidase and amylase. Peripheral blood count showed normocytic anaemia (haemoglobin 9.8 g/dL), thrombocytosis ($482 \times 10^9/L$; normal 150–350 $\times 10^9/L$), elevated red cell volume distribution (70.20 fL; normal 37.1–44.2 fL), high reticulocyte concentration (12.74%; normal 0.90–1.49%) and reduced haptoglobin (<8 mg/dL; normal 30–200 mg/dL).

The peripheral blood count and elevated bilirubin prompted the attending physician to include autoimmune haemolytic anaemias in the differential diagnosis. Microscopic peripheral blood smear showed erythroblasts, marked anisocytosis, numerous polychromatophilic RBCs and few spherocytes. Urinalysis showed no signs of infection; trace urobilinogen was detected.

An abdominal ultrasound was performed due to suspected cholecystitis or cholangitis, which showed only a slightly enlarged spleen (137 mm in length). The other abdominal organs appeared unremarkable.

A chest radiograph was taken to search for the source of the infection, which showed interstitial densities in the upper and partially mediastinal fields of the left lung, with an area of consolidation mainly increased in the perihilar region, and discrete interstitial densities in the mediastinal part of the right lung (fig. 1).

Clarithromycin was empirically included.

Due to the rather extensive inflammatory changes in the lung parenchyma and an enlarged spleen, it was decided to extend the diagnosis with a CT scan of the chest and abdomen. Chest CT showed parenchymal thickening, with air bronchogram in segments 1, 2, 3, 6, and with focal parenchymal destruction and cavities in segment 3 (the largest measuring 14 \times 13 mm) (fig. 2). Tree-in-bud lesions were found in the lingula of left lung. Lesions of similar morphology, as well as peribronchial cuffing in

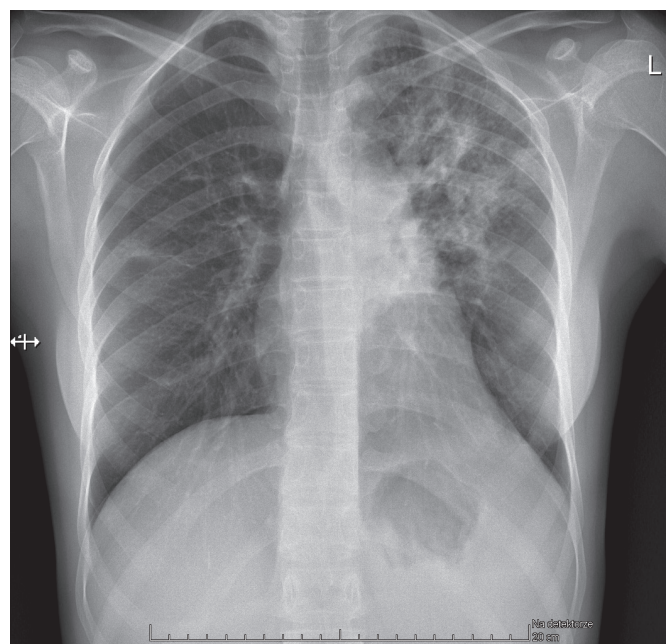


Figure 1. Chest X-ray in the patient before treatment onset

segment 3 were described in the right lung. Parenchymal changes were also visualised in the apices of both lungs. The radiological findings suggested that TB should be considered in the differential diagnosis.

An abdominal CT scan showed an enlarged spleen (up to 140 × 105 mm).

An extended family history revealed that the girl's father had contracted tuberculosis 3 years before.

No Bacille Calmette-Guérin (BCG) vaccination scar was found on physical examination of the girl, despite parental assurances that the child had been vaccinated in accordance with the Ukrainian vaccination programme.

The patient underwent the Quantiferon TB Gold test, which was positive, and the GeneXpert MTB/RIF polymerase chain reaction (PCR) test, which identified the genetic material of *Mycobacterium tuberculosis*, without *RpoB* mutation-associated resistance to rifampicin.

Based on the entire clinical picture, as well as laboratory and imaging findings, pulmonary tuberculosis was diagnosed and hereditary spherocytosis was suspected.

The patient was transported to the Mazovian Centre for Treatment of Lung Diseases and Tuberculosis in Otwock for further diagnosis and treatment. Here, investigations were performed to confirm the presence of TB, i.e. BD MAX genetic testing of sputum and stool, bacterioscopy of sputum and gastric lavage, and conventional culture from the collected material, in which acid fast bacilli were cultured after 3 weeks on sterile media. Once drug susceptibility was confirmed, therapy based on rifampicin, isoniazid, ethambutol and pyrazinamide was administered for two months. An ophthalmological consultation was sought prior to treatment onset to exclude any ophthalmic contraindications. Initially, rifampicin, isoniazid and ethambutol were included, and after two days of good tolerance, pyrazinamide was added.

Three weeks after treatment onset, regression of symptoms such as cough and auscultatory changes over the lung fields was observed. The patient also reported improved well-being and appetite.

A follow-up bacteriological evaluation of gastric lavage one month after treatment onset detected no mycobacteria. It was decided to continue anti-TB treatment with rifampicin/ isoniazid for another 9 months due to the presence of a newborn at home.

After another month, a follow-up bacteriological analysis was performed, showing no mycobacteria in the smear.

Chest radiography performed in the last days of the quadruple therapy showed almost complete regression of parenchymal and interstitial thickening in the right lung and a significant reduction of inflammatory changes in the left lung.

The patient was discharged home in good condition, with the recommendation to continue the above-mentioned

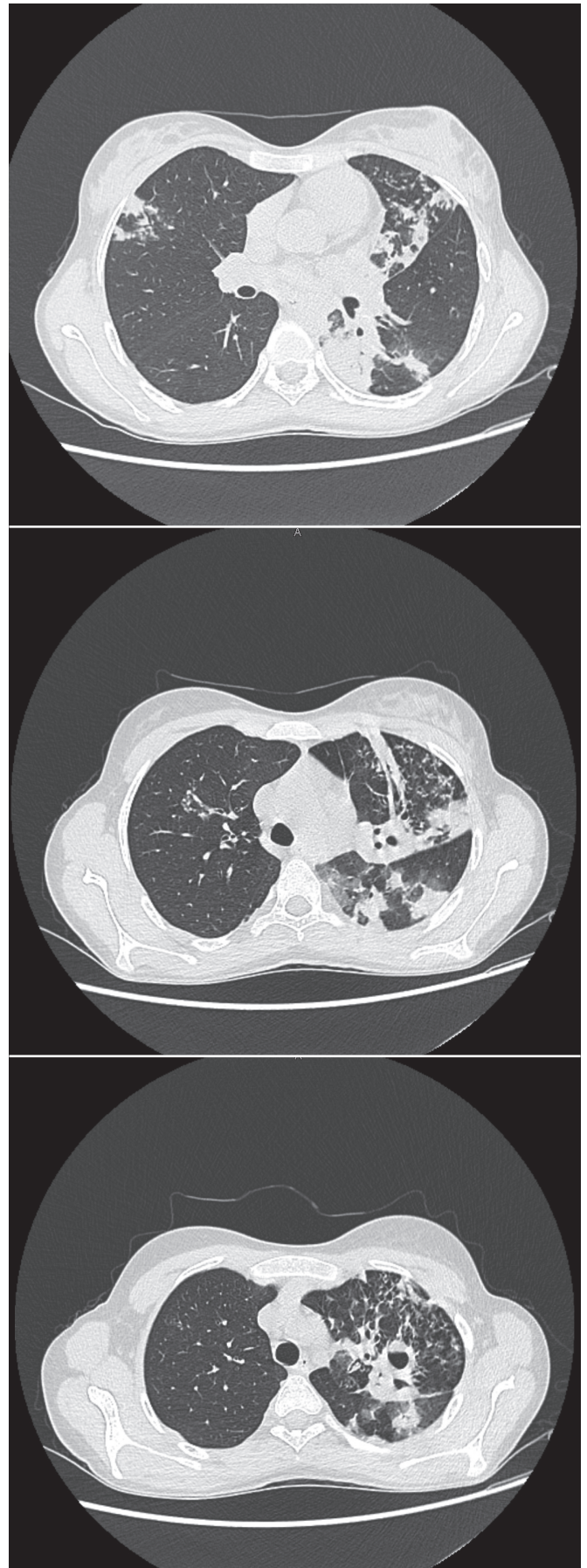


Figure 2. Chest CT before treatment onset. Images taken at different chest levels

medications and to report for a scheduled haematological diagnosis to confirm spherocytosis.

Diagnostic procedures to detect infection in immediate family members confirmed asymptomatic mycobacterial infection in the patient's 5-year-old niece.

Discussion

Every year, tens of millions of children are exposed to *Mycobacterium tuberculosis* infection, with TB remaining a significant infectious cause of mortality in the paediatric population [6]. Children aged 2 to 5 years, closely followed by adolescents (10–18 years), are most likely to be infected [7]. MT is spread through air, mainly by patients with active pulmonary or laryngeal tuberculosis. It is characterised by slow replication and is capable of transitioning to a 'latent' state. Due to young age and, sometimes, immune deficiencies, latent TB may progress to active disease up to many years after the initial infection and despite having received BCG vaccination.

The diagnosis and confirmation of tuberculosis in children is often challenging, even with advanced medical technology. Molecular microbiological methods may fail due to their low sensitivity, especially in the paediatric population. Immunodiagnostic tools are more sensitive, but some of them have low specificity. They also fail to distinguish between active and latent TB, which however can be achieved with tuberculin skin test (TST) and interferon-gamma release assay (IGRA).

Studies have shown that IGRA has a higher specificity than TST in detecting TB infection, particularly in low TB incidence countries and among vaccinated children. Based on a meta-analysis conducted between 2000 and 2011, the specificity of IGRA in TB-vaccinated individuals was estimated at 85–95% vs. 45–60% for TST [8]. The lack of data on the efficacy of IGRAs in children <5 years of age means that these tests are rarely used in this age group [9]. In contrast, TST is used routinely in children as young as 4 to 6 months of age [10]. It is recommended that sputum and gastric lavage be collected for testing in older and younger children, respectively.

Available PCR methods can confirm the presence of mycobacterial genetic material within a few days. However, it should be emphasised that these tests are only complementary to mycobacterial culture. Mycobacterial culture on Löwenstein-Jensen medium allows not only the identification of mycobacteria, but also the assessment of their sensitivity to treatment. Since the sensitivity of mycobacterial detection in the paediatric population using this method is much lower than in adults, the decision to initiate TB treatment should be made before microbiological confirmation. Less than 40% of cases of TB in children are usually confirmed by culture [11].

Latent MT infection is usually diagnosed in the absence of any clinical or radiological signs of tuberculosis. It is recommended that IGRA or TST be performed mainly in children exposed to patients with pulmonary TB, transplant recipients, patients intended to receive TNF- α antagonist therapy and immigrants from high TB incidence countries. According to the experts from the

Centres for Disease Control and Prevention, planned long-term glucocorticoid therapy is also an indication for diagnosis of latent infection [12]. Before performing the above-mentioned investigations, it is reasonable to exclude possible symptoms of active TB, such as chronic cough or subfebrile state, growth and weight gain disorders, and haemoptysis.

Age <5 years, diabetes mellitus, congenital or acquired immune disorders and steroid therapy are factors that increase the risk of developing active TB. After reaching the diagnosis of pulmonary TB, a therapy combining four drugs, each with a different function, is recommended: rifampicin and isoniazid act as bactericides, eliminating bacteria in the replicative phase, while pyrazinamide and ethambutol, which are sterilising drugs, act on the low-metabolism bacterial population. This treatment regimen is prescribed initially for 2 months, followed by rifampicin and isoniazid alone for further 4 months. Transaminases and bilirubin should be measured before treatment onset, especially in patients with liver disease.

If there is a pleural effusion, drainage is required. Treatment of latent tuberculosis can last 6 months and involves regular intake of one anti-TB drug per day, or 3 months with two different anti-TB agents. In some cases, glucocorticoids and pyridoxine may be added to the therapy.

Drug-resistant TB poses one of the biggest challenges in the treatment of MT infection. Multidrug-resistant TB refers to the presence of resistance to at least isoniazid and rifampicin, two of the four key first-line drugs used in standard anti-tuberculosis therapies. Highly drug-resistant TB shows additional resistance to any fluoroquinolone and at least one of three second-line drugs: amikacin, kanamycin or capreomycin. A recent meta-analysis estimated that approximately 3.1% of new TB cases diagnosed in children in 2010 were drug-resistant [13].

Individuals exposed to a patient with an active TB disease are placed under epidemiological surveillance and undergo diagnosis to detect active TB or mycobacterial infection. Isoniazid preventive therapy may be used if necessary. Each confirmed case of the disease must be reported to the Provincial Sanitary and Epidemiological Station.

Research has shown that vaccination significantly reduces the risk of severe forms of TB, such as meningitis and miliary TB, which can be life-threatening in infants. The BCG vaccine is effective in protecting against pulmonary TB in children, but unfortunately its efficacy decreases 10–20 years after vaccination and it no longer provides good protection for adolescents and adults [14]. Work is currently underway to develop a new, more effective vaccine that also protects adolescent patients and produces a long-lasting immune response. Research on the combination of BCG and a subunit vaccine may provide a new immunisation strategy, which could significantly reduce TB morbidity and mortality by 90% and 95%, respectively, by 2035 [15].

Treatment of latent MT infection considerably reduces the risk of developing active disease. Effective treatment of both latent and clinically overt TB may reduce morbidity and mortality in children.

Conclusions

Other possible causes than those currently prevalent in Poland should also be considered when diagnosing infections in immigrants [16]. Differences in clinical manifestations of the disease, as well as language and cultural barriers that may complicate accurate diagnosis and treatment should also be taken into account [17]. The diagnostic and therapeutic process in suspected TB cases requires the use of a wide panel of laboratory and imaging methods and careful analysis of their results. Early identification and precise verification of the pathogen are key to implementing appropriate treatment. Paediatricians, infectious disease specialists and pulmonologists is essential to ensure optimal treatment and control of TB in children. Preventive management and the use of appropriate therapy, in line with current standards, help reduce the spread of TB.

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DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN CARCINOID HEART DISEASE. CLINICAL CASE REPORT

Rakowiakowa choroba serca – trudności diagnostyczne i terapeutyczne. Prezentacja przypadku klinicznego



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Abstract

Neuroendocrine neoplasms develop from diffuse neuroendocrine system cells and occur rare. They characterized by insidious progress and often are recognized accidentally. We present a case of a patient, who had a nephrectomy of the left kidney, due to a papillary carcinoma. While the operation, there had been discovered a focal change of mesenterium, which was taken a biopsy from. On histopathological examination, neuroendocrine neoplasm has been confirmed. The patient was treated with a long-acting somatostatin analogue. During a further observation, progression of the disease has been observed and cardiac metastasis of the neuroendocrine neoplasm was discovered, what is uncommon. Due to progression, peptide receptor radionuclide therapy was added to chronic treatment with the long-acting somatostatin analogue. Stabilization of the disease have been achieved. After 1,5 year the second progression has been observed and the peptide receptor radionuclide therapy was used one more time, which was successful. We also describe a diagnostic difficulty, caused by poor sensitivity of the most often used imaging methods of the heart, like echocardiography and magnetic resonance imaging, which are not as effective as a molecular imaging methods to recognize metastases of neuroendocrine neoplasms. Knowledge about cardiac metastases of neuroendocrine neoplasms still is little. Their impact on a course of disease and prognosis still is not known. For this reason, more investigations are needed.

Streszczenie

Nowotwory neuroendokrynne rozwijają się z komórek rozproszonego układu wydzielania wewnętrznego. Występują rzadko. Charakteryzują się podstępny przebiegiem i często rozpoznawane są przypadkowo. Prezentujemy przypadek kliniczny pacjenta, który przeżył nefrektomię lewostronną z powodu raka brodawkowatego nerki. Podczas operacji wykryto zmianę ogniskową w krezce, z której pobrano wycinki do badania histopatologicznego. Rozpoznano nowotwór neuroendokryny. Zastosowano leczenie długodziałającym analogiem somatostatyny. W dalszej obserwacji podczas progresji choroby wykryto przerzut nowotworu neuroendokryny do mięśnia sercowego, co zdarza się niezwykle rzadko. W związku z progresją do przewlekłego leczenia długodziałającym analogiem somatostatyny dołączono radioizotopową terapię celowaną molekularnie. Uzyskano stabilizację choroby. Po upływie 1,5 roku zaobserwowano drugą progresję choroby i zastosowano kolejny raz radioizotopową terapię celowaną molekularnie, z dobrym skutkiem. W pracy opisujemy również trudności diagnostyczne spowodowane zbyt małą czułością najczęściej stosowanych metod obrazowania serca, takich jak echokardiografia czy rezonans magnetyczny, które ustępują metodom obrazowania molekularnego w zakresie wykrywania przerzutów nowotworów neuroendokryny. Wiedza na temat przerzutów nowotworów neuroendokryny do serca jest nadal niewielka. Nadal nie jest jasny ich wpływ na dalszy przebieg choroby i rokowanie pacjenta. W związku z tym niezbędne jest przeprowadzenie większej liczby badań.

Keywords: neuroendocrine neoplasms; cardiac metastasis; long-acting somatostatin analogue; peptide receptor radionuclide therapy

Słowa kluczowe: nowotwory neuroendokrynne; przerzuty do serca; długodziałający analog somatostatyny; radioizotopowa terapia celowana molekularnie

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Case report

A 68-year-old patient has been under the care of the Department of Endocrinology for more than a decade. At the age of 58 years, the patient, having a history of chronic abdominal pain, weight loss, left lumbar pain, hypertension, nicotine use, chronic obstructive pulmonary disease and gallbladder stones, underwent left nephrectomy due to a tumour of the left kidney (measuring 33 × 45 mm, with central lysis and with enlarged periaortic lymph nodes, detected on abdominal CT scan). During nephrectomy, the tumour (60 mm in diameter) compressing the perirenal and perihilar adipose tissue, was resected. There were no signs of invasion. Intraoperatively, a focal lesion in the mesentery was also detected and sampled. Pathological mesenteric, external iliac, periaortic lymph nodes and metastatic lesions in the liver were detected. Histopathology confirmed a pT1b papillary carcinoma of the left kidney, Fuhrman grade II, G2, while the specimen from the focal lesion was diagnosed as a neuroendocrine neoplasm (NEN G2, Ki 67 5–7%, with positive staining for chromogranin and synaptophysin) (fig. 1).

Two months later, a positron emission tomography/computed tomography (PET/CT) scan with fluorodeoxyglucose confirmed a metabolically active lesion in the small bowel with mesenteric and abdominal lymph node involvement. ⁶⁸Ga-gastrin analogue PET/CT (⁶⁸Ga-PET/CT) detected metastatic lesions in the liver, right renal pole area, mesentery and mesenteric lymph nodes, small bowel, and the skeleton (fig. 2).

Treatment with lanreotide, a long-acting somatostatin analogue, was initiated. The patient was put under surveillance, with monitoring of chromogranin A levels and single photon emission computed tomography (SPECT) findings. Stabilisation of the disease was achieved.

⁶⁸Ga-PET/CT, somatostatin receptor scintigraphy/single-photon emission computed tomography/computed tomography (SRS/SPECT/CT) and CT scans performed in subsequent years did not indicate disease progression (fig. 3).

Treatment with cold somatostatin analogue was continued. Progression was observed five years after the diagnosis of NEN. An increase in chromogranin A from 287.4 ng/mL to 590.1 ng/mL was observed. SPECT/CT somatostatin receptor imaging revealed a new focus in the left part of the heart, at the base of the left ventricle, several pericardial foci, orbital foci and progression of liver and mesenteric lesions (fig. 4 and fig. 5).

Echocardiography raised the suspicion of carcinoid heart disease. Magnetic resonance imaging (MRI) of the heart was ordered due to obesity and difficult examination conditions. It showed an undilated left ventricular cavity, with normal systolic function and an ejection fraction (EF) of 60%, segmental thickening of the septal, anterior and lateral wall up to 22 mm, and impaired blood flow in the thickened anterior/posterolateral wall muscle. The right ventricular cavity was also undilated, with a normal global EF of 57%. Thickening of right ventricular muscle, tricuspid valve leaflets and chordae tendineae (features

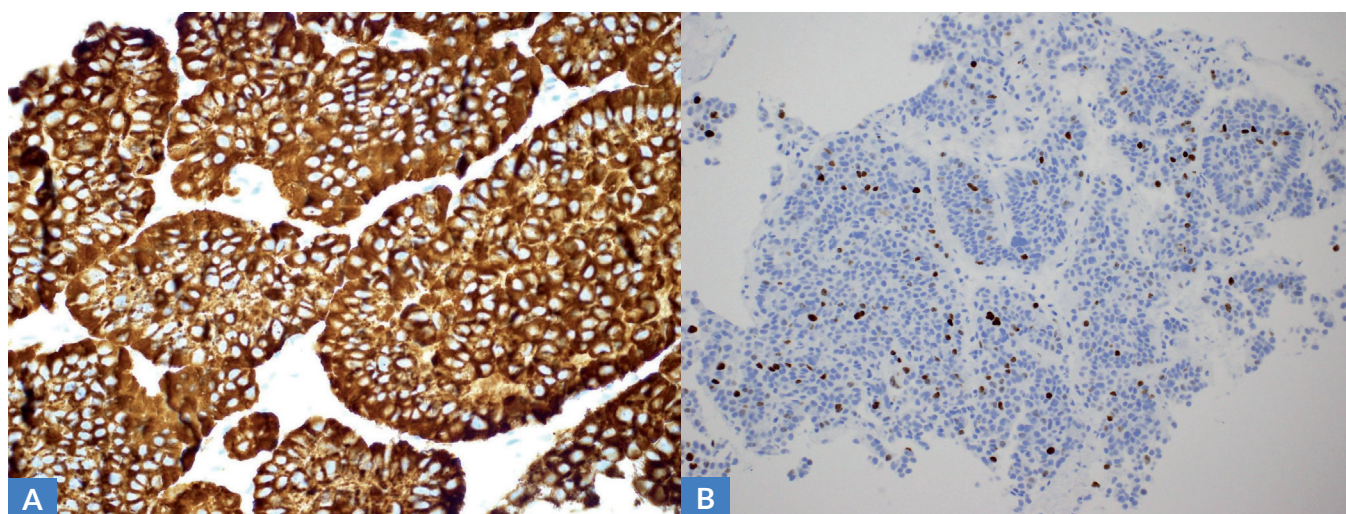


Figure 1. Microscopic image of a section taken from a focal mesenteric lesion. **A.** Positive immunohistochemical reaction with chromogranin (magnification 400 ×). **B.** Approximately 5–7% of tumour cell nuclei were stained in the reaction with anti-Ki67 antibody (clone MIB-1) (200 ×)

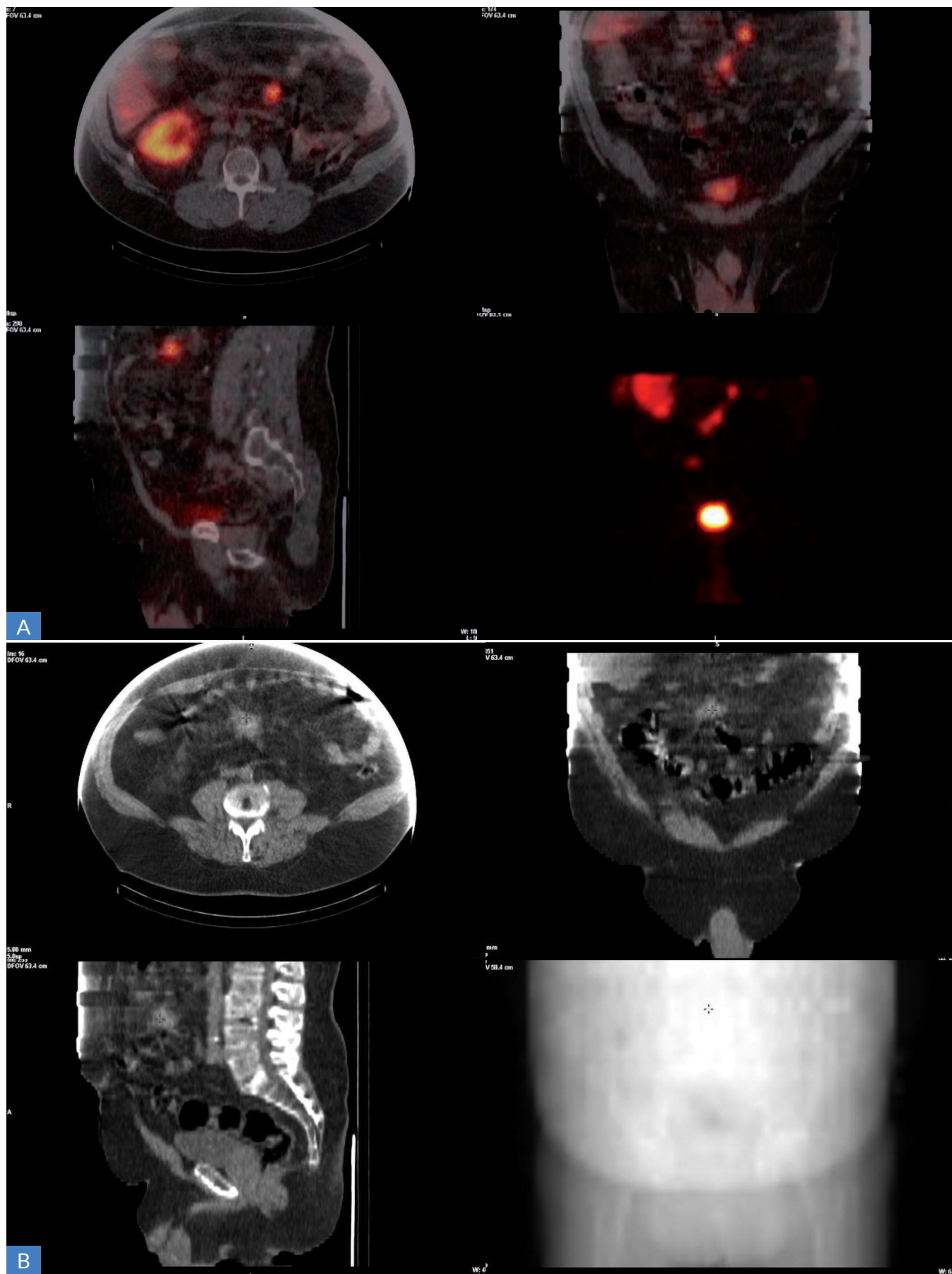


Figure 2. A. ^{68}Ga -PET/CT. A focal lesion in the mesentery with overexpression of type 2 somatostatin receptors was confirmed. Metastatic lesions were found in the liver, the lower pole area of the right kidney, the mesentery, mesenteric lymph nodes, small bowel and skeletal system. **B.** Abdominal CT. A star-shaped focal lesion causing a desmoplastic reaction with calcifications was found in the mesentery

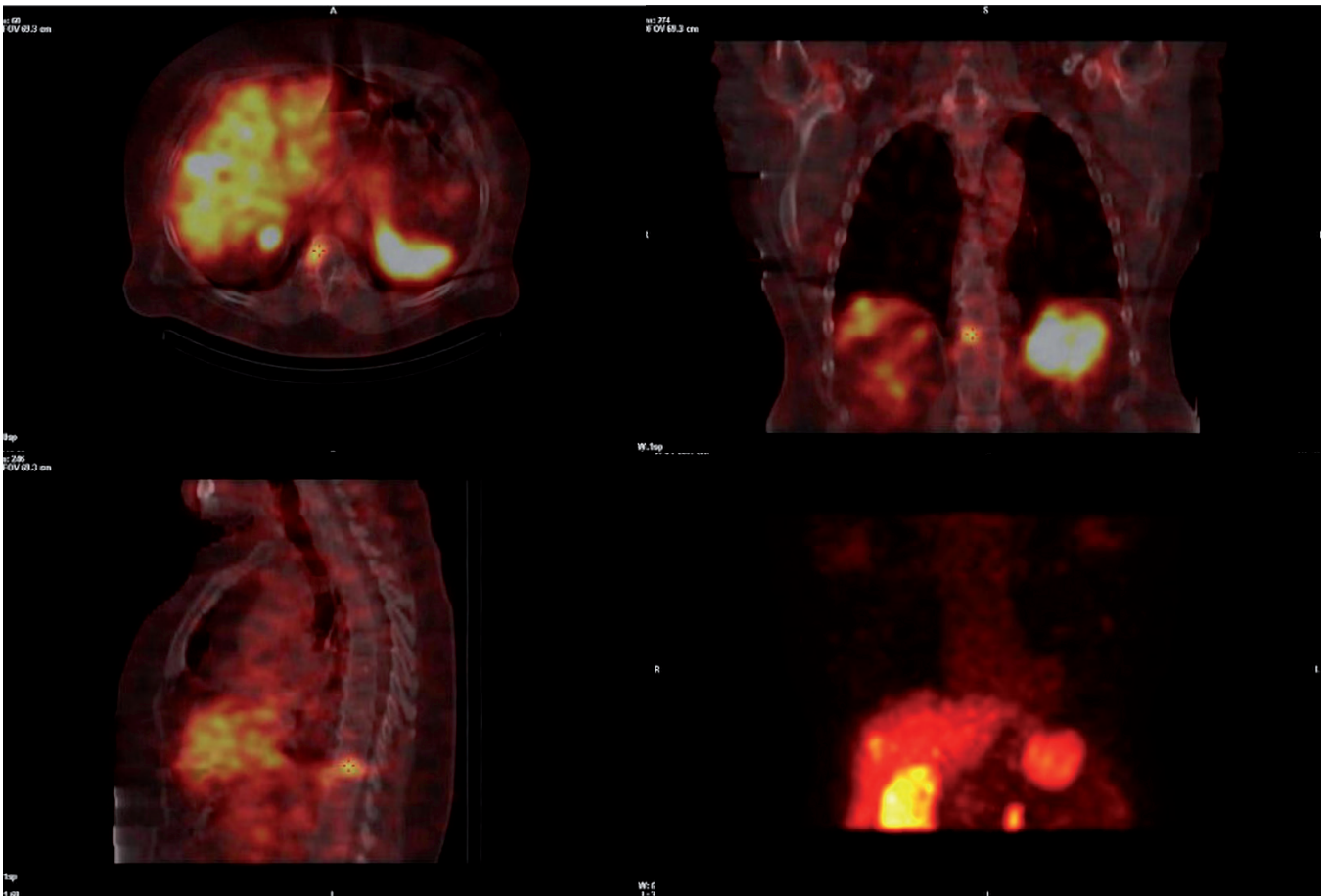


Figure 3. SPECT/CT. Stabilisation of the disease. Pathological overexpression in the liver, mesenteric ileum, at the upper pole of the Th12 vertebra and at the upper pole of the right kidney

of restriction) was observed. There were no myocardial or pericardial focal lesions that would differ in signal on T1-weighted images before and after contrast agent administration. There were no signs of metastatic lesions in the myocardium or pericardium. Late enhancement images after contrast administration showed features of diffuse intramuscular fibrosis in the left and right ventricular muscle; the most severe lesions were located in the thickened muscle in the basal segments of the anterior and anterolateral wall, and in the interventricular septum at the superior and inferior junctions of the right and left ventricles.

Carcinoid heart disease was diagnosed. In view of disease progression, treatment with hot somatostatin analogues ^{177}Lu -DOTA-TADE was administered and long-acting somatostatin analogue was continued. The patient underwent four cycles of peptide receptor radionuclide therapy (PRRT). A total of four 200 mCi cycles of ^{177}Lu -DOTA-TADE were administered and disease stabilisation was achieved. At follow-up 1.5 years after the last administration of PRRT, a ^{68}Ga -PET/CT scan was performed, diagnosing overexpression of somatostatin receptors in the mediastinal lymph nodes and right orbit, multiple foci in the skeleton, infiltrative lesions in the mesentery of the intestine, and two foci in the myocardium (fig. 6).

A 24-h urine collection showed increased 5-hydroxyindoleacetic acid (5-HIAA) excretion (63.1 mg/day [normal 0.5–9 mg/day]) and excluded increased metoxy catecholamines excretion. Echocardiography showed no organic

changes or haemodynamically significant valvular defects, no features of cardiac carcinoid disease and failed to visualise the described intracardiac metastatic lesions. Chromogranin A increased from 687.6 ng/mL to 1704.0 ng/mL over a period of 7 months. Further disease progression was observed. The patient was not qualified for mTOR inhibitor treatment due to lack of reimbursement for the treatment and the location of the primary lesion, and was qualified for repeat PRRT instead. The patient received further four cycles of treatment, achieving disease stabilisation (fig. 7).

Discussion

The case presented here demonstrates the importance of adequate therapy and an individualised approach to a NEN patient.

Metastatic cardiac tumours (MCTs) are rare, detected in 1.5–20% of autopsies of cancer patients. They are usually clinically silent. Although any cancer can lead to distant cardiac metastases, melanoma, lymphomas, leukaemias, lung, breast and oesophageal cancers are most likely, whereas intracardiac NEN metastases are very rare [5].

In the case of NEN, cardiac metastatic lesions are extremely rare due to the frequency of these tumours. The liver and lymph nodes, followed by the skeleton, lung and peritoneum, are the most common NEN metastasis sites [5]. In recent years, less common metastatic sites

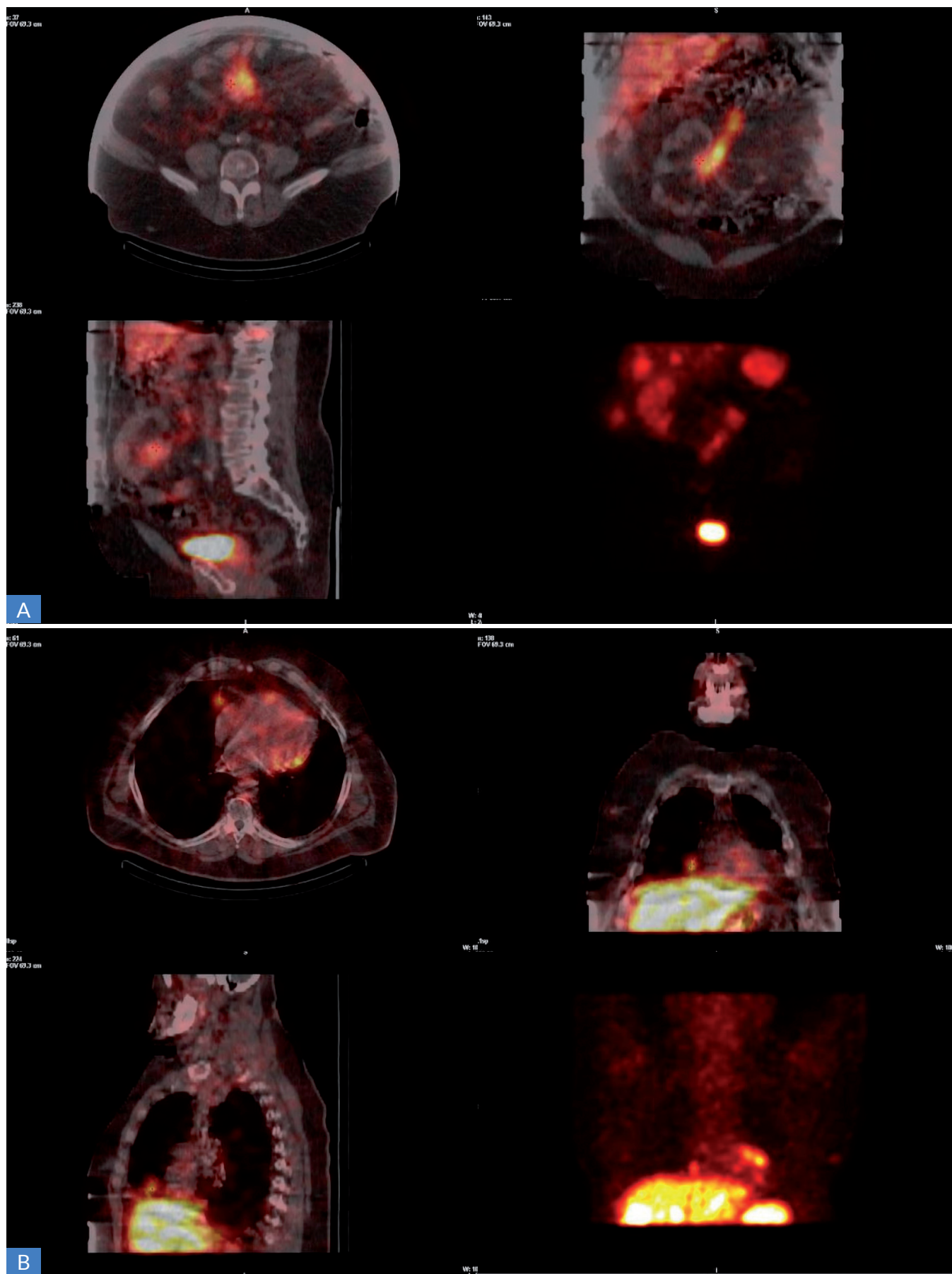


Figure 4. SPECT/CT. Progression of the disease. **A.** Pathological overexpression in the liver, intestinal mesentery, at the upper pole of the right kidney and in the Th12 vertebral body. **B.** Additional focal lesions in the heart, orbits, subcutaneous tissue of the chest (in the right breast view); progression of liver lesions

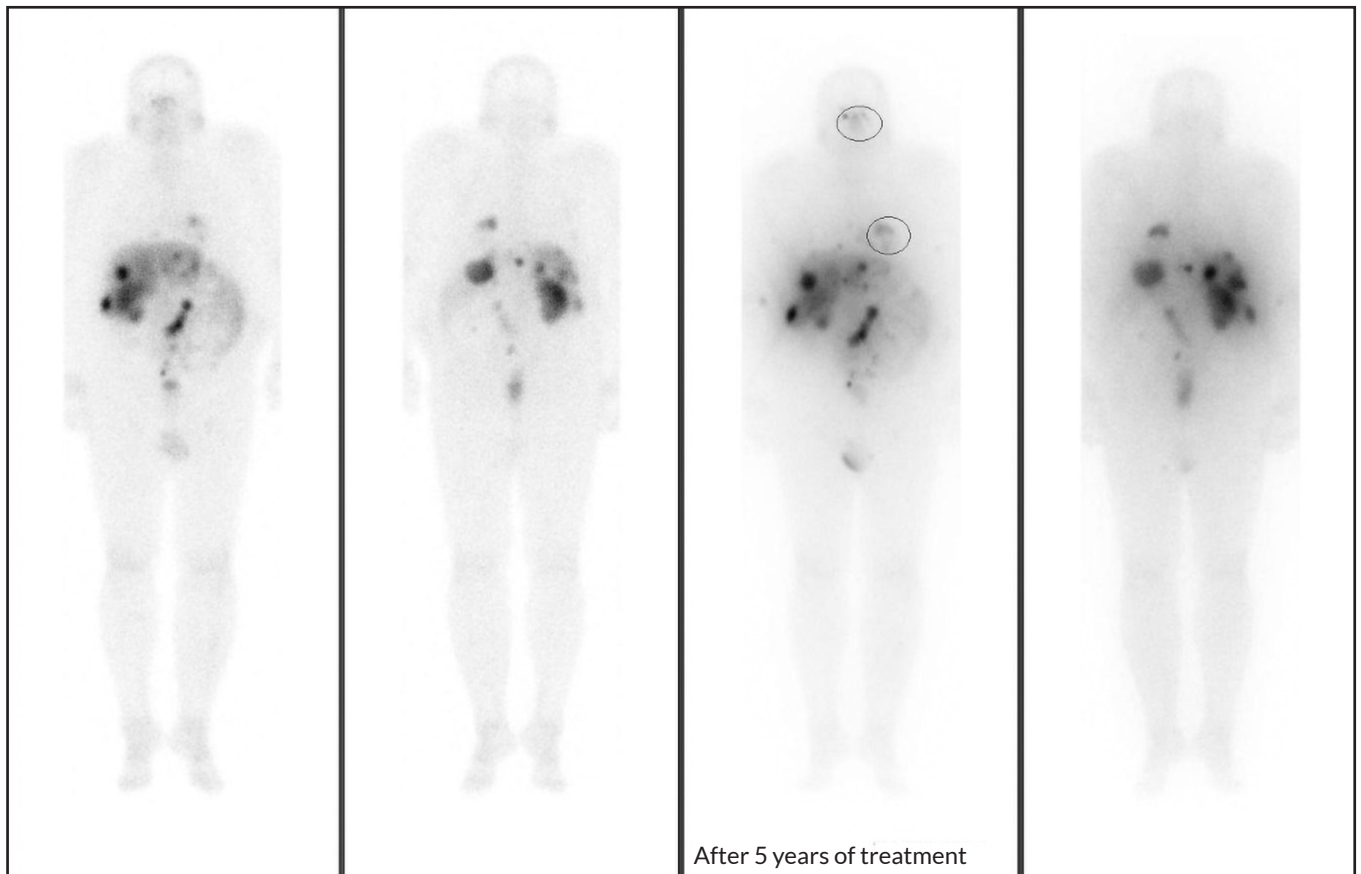


Figure 5. Somatostatin receptor scintigraphy (SRS). Evident progression of lesions after 5 years of treatment with a long-acting somatostatin analogue. Additional focal lesions in the heart, orbits, subcutaneous tissue of the chest (in the right breast view); progression of liver and mesenteric lesions

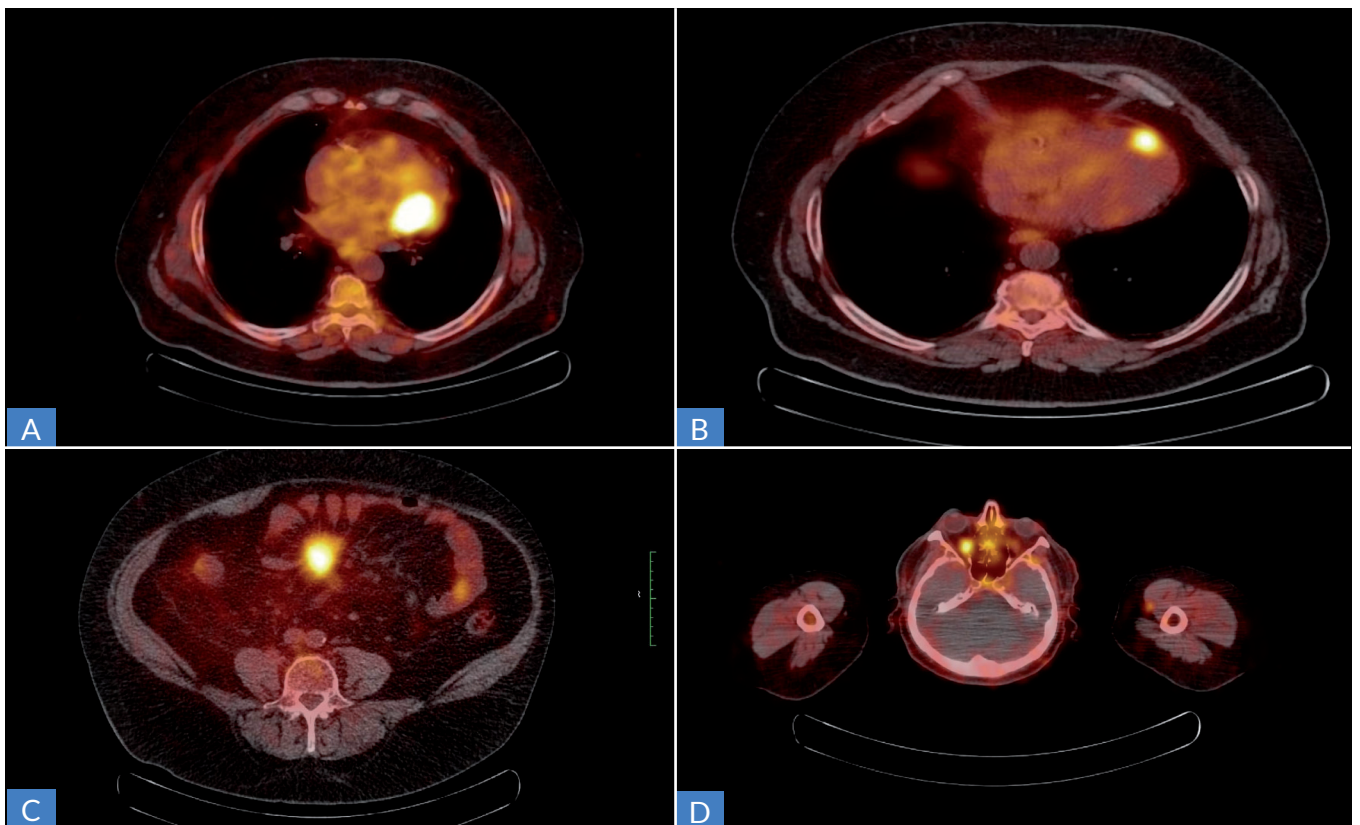


Figure 6. ^{68}Ga -PET/CT. Overexpression of somatostatin receptors. **A, B.** Two focal lesions in the myocardium. **C.** A focal lesion in the mesentery of the small intestine. **D.** A focal lesion in the right orbit



Figure 7. Follow-up scintigraphy after the second treatment cycle with hot somatostatin analogues. Stable lesions. No new foci of increased pathological radiotracer accumulation

such as the brain, breast, ovaries, adrenal glands, skin or heart have been increasingly reported due to advances in molecular imaging. Echocardiographic detection of cardiac metastatic lesions is difficult, mainly because lesions smaller than 10 mm are not visible. Although cardiac MRI is the imaging modality of choice in the assessment of tumours and myocardial invasion, the case described here shows that it has lower sensitivity compared to molecular imaging methods. Somatostatin receptor scintigraphy has a high sensitivity and allows imaging of metastatic lesions that are not visible with other methods. ^{68}Ga -PET/CT remains the tool with the highest sensitivity in NEN imaging.

To date, only one meta-analysis has been conducted on the incidence and location of intracardiac metastases arising from NEN, as well as their impact on ejection fraction and survival rates. In this study, conducted by Hamza et al., cardiac metastatic lesions were found in 2.3% of patients (257 cases) out of the 16,685 NEN cases analysed. These lesions were most often detected by ^{68}Ga -PET/CT. The left ventricle (48%), followed by the pericardium, right ventricle, interventricular septum, left atrium, and right atrium, was the most common site of intracardiac NEN metastases. Reduced EF, occurring in 15% of patients, was the most common clinical manifestation of intracardiac NEN metastases. However, the majority of patients did not have reduced EF excluded before the diagnosis of cardiac metastases. The mean survival of patients from the time of intracardiac NEN metastasis diagnosis was 35.89 months. In the case presented here, the patient has lived for more than seven years since the diagnosis of metastatic lesions. He does not present with cardiac arrhythmias or symptoms of heart failure.

Conclusions

Intracardiac NEN metastases are very rare and usually asymptomatic. Their detection may require the use of imaging modalities with the highest sensitivity, such as ^{68}Ga -PET/CT. There are no precise data on their possible impact on myocardial complications, such as arrhythmias, conduction blocks, heart failure, valvular defects or acute coronary syndromes. Further studies are needed to determine the definitive impact of cardiac metastases on the survival of NEN patients.

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