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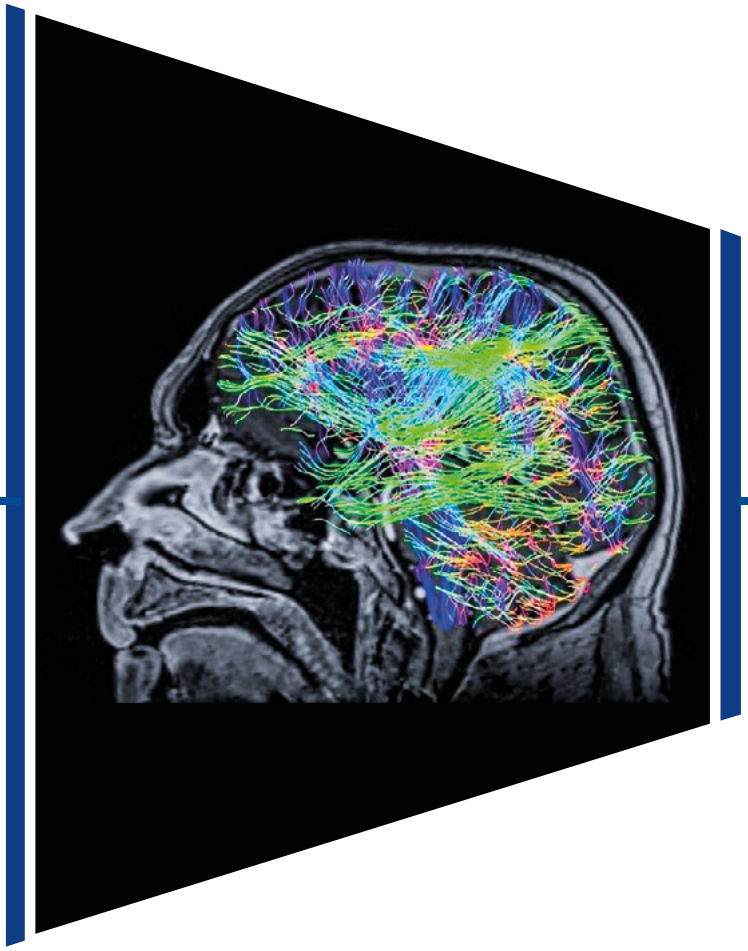

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Editorial Office

Department of Cardiology
and Electrotherapy
Medical University of Gdańsk
Dębinki 7
80-211 Gdańsk, Poland

Phone: +48 58 349 39 10
Fax: +48 58 349 39 20
E-mail: ejtcm@gumed.edu.pl
www.ejtcm.gumed.edu.pl

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INVITED REVIEW ARTICLE

The problem of paediatric patients in developing countries: do we actually know how to feed the malnourished children?

Daniel Kasprowicz, Franco Cyrille Rajaomalala

Medical Clinic *Flamboyant*, Mampikony, Madagascar

Abstract

The problem of malnutrition affects both developed and developing countries. The disease-related malnutrition in hospitalised patients is well-described and the treatment recommendations reflect the health care conditions of developed countries. However the diagnosis and treatment of children with severe acute malnutrition (SAM) is inconsistent both in the international and in the developing countries' guidelines. The aim of this article is to start a discussion about the guidelines for the treatment and nutrition of malnourished infants and children in developing countries. The differences appear primarily in the hydration and nutritional status assessment, treatment of hypoglycaemia, additional supplementation and partly in nutrition itself. In general, we do know how to treat children with SAM, however the differences in the guidelines can cause a lot of difficulty in making decisions in emergencies, particularly for infants under 6 months.

Keywords: severe acute malnutrition · infants · supplementation · nutritional status assessment · WHO protocol

Citation

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Introduction

The problem of world hunger is not new, however the recent trends in global food security force us to ask questions about the effectiveness of international interventions. Although the newest United Nations Food and Agriculture Organisation (FAO) statistics show a clear distribution of malnourished people in different regions of the world, the data also indicate that we are not winning the battle with famine. Furthermore, since 2014 the fight against hunger seems to be moving towards global failure with a large increase in people suffering from overweight and obesity [1]. In developed countries malnutrition is related with chronic or acute disease and most often affects hospitalised patients (20 to 50% of patients, depending on the hospital department or the nature) [2-3]. Therefore, hunger result-ing from food insecurity is rather the domain of

Corresponding author:
Daniel Kasprowicz, Medical Clinic *Flamboyant*, Mampikony, Madagascar
e-mail: d.kasprowicz1990@gmail.com
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developing countries, mainly countries in sub-Saharan Africa, Central Asia and Southern Asia. Statistically, 25.9% of the African population does not have adequate access to nutritious food and 30.3% of children < 5 years of age are malnourished [1]. Moreover, statistics do not include micronutrient-related malnutrition and micronutrient excess, which may suggest that malnourishment is a bigger problem quantitatively [4]. The quick progress of knowledge in nutritional sciences, development of nutritional status assessment methods and nutritional risk, accessibility of artificial diets and nutritional teams enabled effective treatment of disease-related malnutrition [5-13].

However, using the developed countries' standards to treat and feed malnourished patients in developing countries is impossible due to the insufficient quantity of ready-to-use therapeutic food (RUTF) and oral nutritional supplements (ONS), lack of medical and technological resources, low financial support and inadequate training of health workers. Although the World Health Organisation (WHO), UNICEF or Doctors without borders (*Médecins sans frontières*, MSF) published several guidelines and assessment tools, many of the presented algorithms for the treatment of malnutrition are still not implemented [14-16]. Among the reasons for this situation is the complex task of adapting the guidelines to the local resources and capabilities, the co-occurence of malnutrition and tropical diseases and the relatively scarce evidence base for the treatment of malnutrition of infants < 6 months of age [17-18]. In addition, many of the countries struggling to provide effective care for the malnourished paediatric patients also lack funding for research, hence the specific and critical research questions regarding the nutrition or nursing care (which are not yet addressed by the aforementioned guidelines) remain unanswered and the evidence base remains scarce.

The aim of the article is to start a discussion about the treatment and nutrition of malnourished infants and children in developing countries. In addition, it is important to note the lack of specific nutrition standards and lack of consistent international guidelines, especially among children < 6 months of age. The authors would like to emphasize that this article is not intended to suggest standards for the treatment of malnourished children in developing countries.

Nutritional Status Assessment

Accurate nutritional status assessment (NSA) is the first and key element in the diagnosis of severe acute malnutrition (SAM) in paediatric patients [19]. SAM consists of two basic forms: severe wasting (also described as marasmus or energy malnutrition) and nutritional oedema (also described as kwashiorkor or protein malnutrition). Marasmus is a consequence of uncomplicated prolonged starvation. It is mainly characterised by a decrease in body weight and other anthropometric and immunological indicators. Usually, total protein and serum albumin are normal or slightly below normal. There is also a shortage of minerals and vitamins such as iron, iodine, zinc and vitamin A. Kwashiorkor is a result of hypercatabolism due to qualitative and quantitative malnutrition. Patients have a decrease in protein fractions in the blood serum, which results in oedema and apparent weight gain [1, 14-15, 20-21]. Both types of malnutrition can also be caused by bacterial, viral and parasitic infections or by the combined burden of malnutrition and tropical diseases [22]. WHO also distinguishes a third type: marasmic kwashiorkor characterised by a decrease in muscle mass and fat, sarcopenia, weakening of the im-mune system, anaemia, lowering of protein levels in blood serum, digestive and absorption disorders as well as impairment of organs and body systems [15, 20-21].

Criteria for pharmacological and nutritional treatment of SAM

Although the scientific societies established several criteria for diagnosing malnutrition, none are specific to children < 6 months. Using different methods of NSA in the same group of patients, we can obtain significant differences in the percentage distribution of well-fed and malnourished patients [2]. This poses the risk of not diagnosing early malnutrition, which may manifest with symptoms or biological changes not included in the basic parameters of the selected NSA method [15]. A special treatment algorithm is intended for children with SAM. Some recommendations suggest using selected algorithms also to treat children with moderate acute malnutrition (MAM), but NSA determined by different methods can lead to the exclusion of some paediatric patients [14-17].

The most popular and oldest method of NSA among paediatric patients is to determine abnormalities in weight and height/length on percentile charts regarding weight-for-height/length, however since 2005 the WHO recommends that mid-upper arm circumference (MUAC) and the occurrence of oedema as independent diagnostic indicators of malnourishment [2, 23-24]. The index of weight-for-height/length primarily gives information about weight loss compared to children with good nutritional status of the same height/length. MUAC indicates loss of muscle mass and gives quick

check of infants and children's nutritional status [14]. Comparing these two measurements, MUAC seems to play a more important role because it is a more reliable parameter, burdened with less risk of incorrect measurement, and can also be used by minimally-trained non-professionals for community-based screening of SAM in infancy [25]. WHO, UNICEF and MSF unanimously propose that in developing countries for the diagnosis of SAM and thus for pharmacological and nutritional treatment, children should meet the criteria:

- the MUAC in infants and children 6-59 months is <115 mm,
- and/or bilateral pitting oedema,
- and/or a weight-for-height/length < 3 Z-score of the WHO growth standards

Some recommendations suggest MUAC < 110 mm, but using this criteria may lead to under-diagnosis. Besides proper anthropometric parameters attention should be paid to other elements that may be the first symptoms of micronutrient-related malnutrition and micronutrient excess. During the history-taking, it is worth asking about the current diet and breastfeeding time, birth weight, vaccinations, episodes of diarrhoea and vomiting, urine colour, and contact with people suffering from infectious diseases. In physical examination, it is important to check the basic life parameters, size of the liver and spleen, peristalsis sounds on auscultation, skin pallor, signs of circulatory collapse and any changes in the eyes, ears, skin and hair [14-17, 25-26]. The circumference of the child's head is not recommended because of statistically significant variation within nations and ethnic groups, leading to overdiagnosis of macrocephaly or microcephaly may occur. Also, growth percentiles charts may not be optimal in all cases and a very careful and individual examination is required [27].

SAM in infants under 6 months of age

For many years, the issue of diagnosing and treating malnourished infants under 6 months of age was underestimated, and in international and national guidelines little or no attention was paid to it. Furthermore, each guideline points to completely different factors causing malnutrition as well as factors affecting the treatment process. Using the guidelines to make the decision to hospitalise an infant patient is also difficult. The criteria that are strongly recommended for defining SAM and MAM in infancy and for starting a nutritional intervention are:

- weight-for height/length < 3 Z-score of the WHO growth standards,
- and/or the presence of bilateral oedema.

Other parameters which are worth attention:

- infant is too weak to be breastfed,
- and/or insufficient milk production by the mother,
- and/or body length below 49 cm,
- and/or the infant has not gained any weight within 1-2 weeks,
- and/or weight loss has been observed.

So far no recommendation was made to divide SAM into complicated and uncomplicated forms [17]. Some recommendations suggest that patients < 3 kg [17, 28-36] or < 4 kg [37-38] should be treated and fed as patients under 6 months. None of the guidelines focus on NSA of infants < 6 months. Studies show that scales used in nutrition-related emergencies are largely unsuitable for weighing infants < 6 months [39]. International and national guidelines also does not recommend MUAC for NSA of infants under 6 months [17], but independent medical institutions pointed to MUAC as a simple and easy method for quickly diagnosing infants with MAM and SAM [25].

Nutritional and pharmacological treatment

The comprehensive treatment of a malnourished child consists of three phases: initial treatment (also referred to as stabilisation phase; up to 7 days), rehabilitation (2-6 weeks) and continuation of treatment including emotional stimulation and sensory development of the child. In terms of nutrition, the first phase is the most important and contains many tasks that must be undertaken by a physician, a dietitian or a nurse, e.g. treatment (or prevention) of hypoglycaemia, hypothermia and dehydration, water and electrolyte imbalance, treatment of possible infections, careful start of nutrition as well as diagnosis and treatment of comorbidities (e.g. vitamin deficiency, heart failure or anaemia) (Figure 1) [17, 26, 40].

Hypoglycaemia

Hypoglycaemia in children with SAM is diagnosed when blood glucose level is < 54 mg/dL (< 3 mmol/L), but MSF suggests intervening in blood glucose < 60 mg/dL (< 3.3 mmol/L) [26]. Severe hypoglycaemia is a condition when the blood glucose level is < 40 mg/dL (< 2.2 mmol/L) [14]. The most common causes of hypoglycaemia in children with SAM or MAM are:

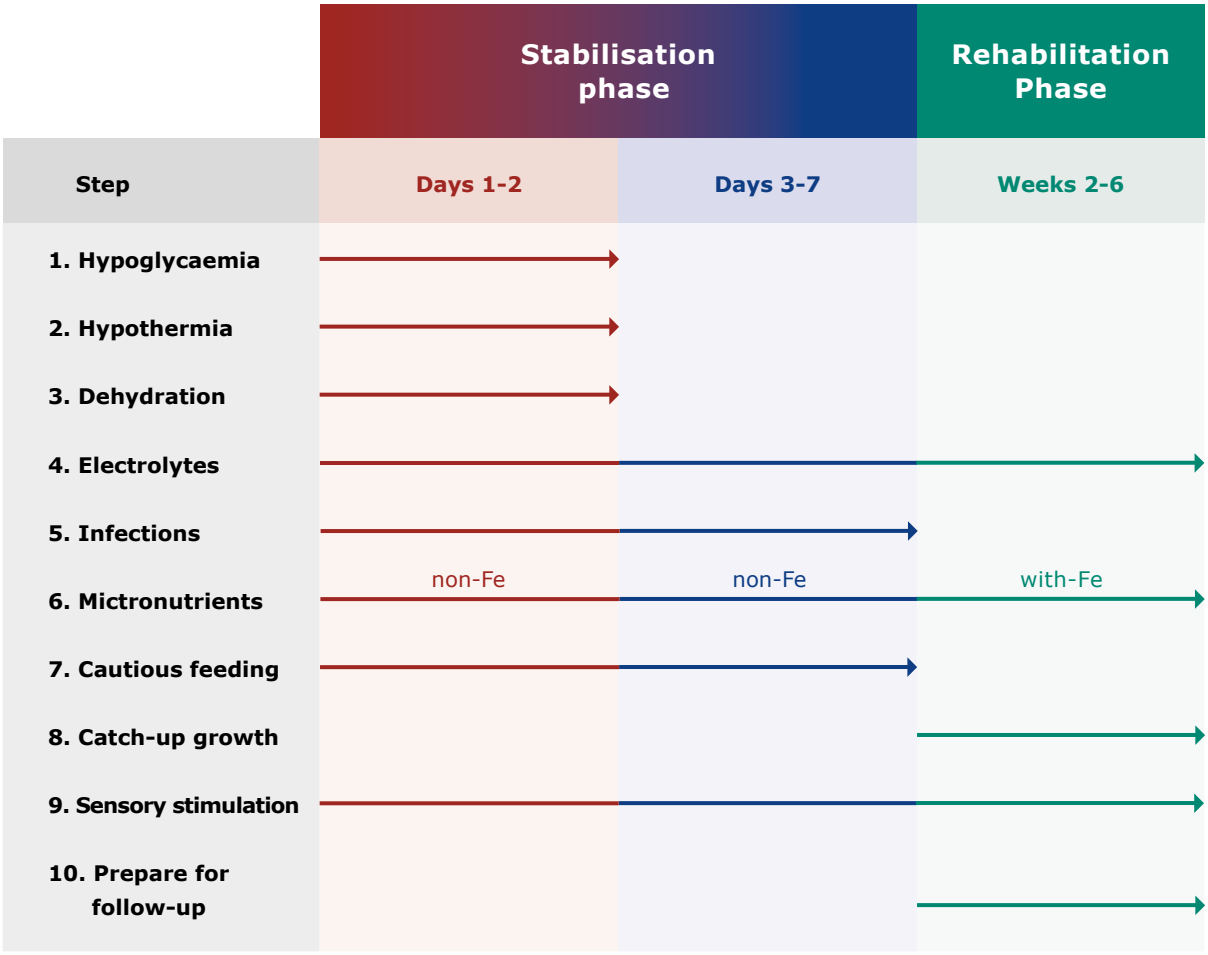

Figure 1. Main steps in the treatment of SAM

Source of data: WHO [14]

- a reduced amount of stored glucose in the muscles (decrease in muscle mass, wasting),
- weakening of glucose conversion mechanisms (due to increased metabolism of proteins and fats),
- immune response to infection (including the particularly dangerous *Plasmodium falciparum* infection),
- impaired glucose absorption in the gastrointestinal tract (atrophy of the intestinal villi, gastrointestinal mycosis),
- prolonged fasting and delayed introduction of nutrition (due to the long journey to the hospital) [26, 41-43].

If hypoglycaemia occurs in a child with SAM, immediate intervention should take place because this is the main cause of death in the first phase of treatment. If it is not possible to check the blood glucose level, it is recommended to administer prophylactic glucose solutions based on clinical symptoms [26]. Treatment of hypoglycaemia in the most common conditions is presented in Table 1 [14, 16-17, 26].

Table 1. Management of hypoglycaemia in various states

Statement	Intervention	Comments
Unconscious / convulsive child	5 ml of 10% sterile glucose i.v./kg body weight (2-3 minutes)	1. Check the glucose level after 15 minutes. If blood glucose level is still below the norm, give an another bolus. 2. After regaining consciousness, feed with F-75[A] diet. 3. If there is no improvement, rapid diagnosis for another factors causing hypoglycaemia *

Unconscious child with a nasogastric tube (NG)	5 ml 10% sterile glucose per kg body weight i.v. (2-3 minutes) and then 50 ml of 10% solution of glucose or sucrose by NT	1. If vascular access is not available, 50 ml of a 10% glucose or glucose solution should be first administered via the NG 2. After regaining consciousness, feed with F-75 diet or glucose dissolved in water (60g/L) 3. If there is no improvement, rapid diagnosis for another factor causing hypoglycaemia *
Conscious child, without NG	50 ml of 10% glucose or sugar solution orally, next start F-75 diet every 30 minutes for the next 2 hours. Then give a meal rich in complex carbohydrates.	1. If there is no improvement, rapid diagnosis for another factor causing hypoglycaemia *
Infant <6 months	Diluted F-100[B] **	No information provided

*** No clinical improvement may suggest severe infection (e.g. malaria, meningitis) or epilepsy. Perform a quick diagnostic test and then apply the appropriate treatment (antibiotic therapy, anti-malarial therapy, anti-epileptic therapy) with the symptomatic treatment of hypoglycaemia.**

**** MSF 2006 recommendation for the prevention of hypoglycaemia in children with SAM. However the WHO, MSF and UNICEF guidelines do not include specific recommendations for the treatment of hypoglycaemia in infants < 6 months of age.**

[A] Formula 75; therapeutic milk, 100 ml of F-75 provides 75 kcal and 1 g of protein

[B] Formula 100; therapeutic milk, 100 ml of F-100 provides 100 kcal and 3 g of protein

There are infections that can significantly lower blood glucose levels, and thus reduce the effectiveness of conservative treatment. In the case of malaria (*P. falciparum*) infection, there is a decrease in blood glucose as a result of multi-enzymatic changes caused by infection and simultaneous starvation on the one hand [44-45], and on the other hand the treatment with quinine or quinidine leads to hyper-insulinemic hypoglycaemia [46-47]. It is recommended to administer either drug by constant infusion with 5% glucose, active feeding during the disease and regular glucose measurement [14].

Hydration status assessment

Hydration status assessment (HSA) of malnourished paediatric patients is very difficult due to the differences in the dehydration symptoms in different types of malnutrition. Furthermore, it is often difficult to determine the acute symptoms of dehydration and chronic symptoms of malnutrition. Dehydration is a serious health problem in the first phase of treatment and just like hypoglycaemia, it is one of the main causes of death in the course of MAM or SAM. The most severe complication is severe hypovolemic shock [14, 17]. MSF and WHO suggest dividing patients into three groups: no signs of dehydration, moderate dehydration, and severe dehydration. More specific differences and assessment of dehydration severity are included in Table 2 [16, 48]. Matiland et al asked a bold question whether the risk of death in children with SAM could be identified using WHO protocols. In children with diarrhoea, hydration status was of limited importance as a prognostic symptom because only 58% of deceased children were assessed as moderately or severely dehydrated. CRT best identified the high risk of death [49]. In properly hydrated patients, oral rehydration salts (ORS) are used to prevent dehydration. In children < 2 years of age it is recommended to administer 50-100 ml after each stool until diarrhoea disappears. In moderately or severely dehydrated patient without hypovolemic or septic shock, it is recommended to give ORS 5-10 ml/kg/h for up to 12 hours orally. In case of swallowing

Table 2. Hydration status assessment

Parameter	Normal	Moderate dehydration	Severe dehydration
Awareness	Normal	Confused	Sleepy or unconscious
Subcutaneous tissue	Tense	Sunken around the eyes	Sunken around the eyes, sunken fontanelle
Capillary Refill Time	Normal	< 2 sec	> 2 sec
Thirst	Normal	Intensified	Intensified or none
Heart Rate	Normal	Tachycardia	Tachycardia, cooling of the peripheral parts
Pulse	Easily palpable	Palpable	Difficult to palpate
Weight Loss	< 1%	1-5%	5-10%
Other	Person drinks normally	History of watery stools	(1) Hypotension, (2) Loss of tears, dry tongue, reduced diuresis, (3) watery diarrhoea (> 3x loose, watery stools/day) is a specific parameter

difficulty, fluids administration via nasogastric tube is recommended. For patients with complications, it is worth using the algorithm proposed by MSF suggesting the intravenous administration of a sterile solution of Ringer Lactate-Glucose 5% (RL-G%) [16]. Hydration is based on the daily hydration requirement (DHR) presented in Table 3 [16]. In the case of significant weight loss due to dehydration, it is recommended to multiply the DHR by 1,5. If RL-G5% is unavailable, it is recommended to prepare your own formula by adding a sterile 50% glucose solution to 500 ml RL. If RL is unavailable, 0.9% saline may be used [16-17, 26]. Many national and international guidelines are based on the WHO recommendations from 1999 and still suggest to treat severe dehydration with intravenous half-strength Darrow's solution with 5% glucose (dextrose) as the first choice and 0.45% (half-normal) saline with 5% glucose with 20 mmol/L potassium chloride [14, 17]. In contrast, the more recent WHO guidelines from 2013 recognised the aforementioned recommendations as a conditional

Table 3. Daily hydration requirements

Weight [kg]	Dosage
0-10	100 ml/kg per day
11-20	1000 ml + (50 ml/kg for every kg over 10 kg) per day
> 20	1500 ml + (20-25 ml/kg for every kg over 20 kg) per day

Source of data: MSF guidelines [16]

choice, and that the evidence for the effectiveness of such treatment is of very low quality. This was due to the limited availability of randomised controlled trials, trials comparing existing WHO recommendations with new treatment options, or trials documenting comparisons of diagnoses and treatment methods [26].

There are no specific guidelines for HSA in children < 6 months. Nevertheless, the MAMI report indicates that the WHO, UNICEF and MSF guidelines can also be used in newborns [17]. It is important to monitor progress during hydration (pulse rate, respiratory rate, urine frequency, stool/vomit frequency) every half hour for the first 2 hours and then every hour for 6-12 hours. In addition, the appearance of tears, moisture in the mouth, shortening of CRT, reduction of the collapse of the fontanelle and eyes may indicate a positive hydration process. However, attention should be paid to chronically malnourished patients, because even after adequate hydration these features may remain unchanged. There is a huge risk of over-hydration, which can also be fatal [50]. The 2006 MSF Nutrition Protocol highlights fluid therapy for watery diarrhoea. In diarrhoea without dehydration and without above-mentioned features, ORS are not advised and frequent oral hydration with water is recommended, not ORS. In the case of aversion to drinking plain water, the guidelines recommend oral administration of 50 ml of a 10% sugar solution after each loose stool and HSA every 4 hours, mainly controlling weight loss. The goal of this procedure is to avoid complications associated with hydration, mainly over-treatment with fluids [48].

An important element in the treatment of dehydration associated with severe diarrhoea is additional zinc supplementation. In international and national guidelines, supplementation with this element was limited to the use of rehydration solution for malnutrition (ReSoMal), which contains 0.3 mmol of zinc per litre of solution [16-17]. MSF Nutrition recommends supplementation with 10 mg zinc for 10 days in children < 6 months, and 20 mg zinc for 10 days in children > 6 months [48]. Many randomised studies have demonstrated the effectiveness of additional zinc supplementation in children > 6 months of age, but the significance in children < 6 has been questioned [51-53].

Additional supplementation

Serum levels of vitamin A, folic acid (FA) and iron should be laboratory checked in malnourished children, even if there are no clinical signs of deficiency [48]. Despite the recommendations to monitor these three micronutrients, especially in children with SAM > 6 months [17], the lack of access to medical laboratories, qualified laboratory personnel and medical equipment creates a significant barrier in Sub-Saharan Africa [54]. Thus, in many cases the deficiencies of these components are determined when significant clinical symptoms already occur and often are very difficult to treat with inexpensive medicaments or when the patient is acutely ill. This is the a paradox of the requirements imposed by the guidelines of global organisations that cannot realistically be met in underfunded and underequipped health care facilities in developing countries.

Vitamin A

Supplementation with vitamin A, and its derivatives are used to prevent xerophthalmia and blindness, and to treat malnutrition and intestinal diseases. The incidence of infectious diseases decrease, and indirectly the mobility reduction, could be obtained through vitamin A related to gut immune tolerance/homeostasis, intestinal barrier integrity, and responses to enteropathogens in the context of the environmental enteric dysfunction [55-60]. The MSF Nutrition Protocol recommends a single dose of 100,000 IU for children 6-12 months and 200,000 IU for children > 1 year [48]. 8 of 14 international guidelines and 15 of 23 national guidelines[1] suggest supplementation of 50,000 IU vitamin A once orally on the first day of admission in children < 6 months [17]. A 2003 WHO report states that supplementing 5,000 IU of vitamin A daily during the hospital stay yields much better results than a single dose of 100,000 IU. This method of supplementation prevents severe diarrhoea and respiratory diseases. A single dose seems to bring good results only during measles, in ongoing infectious diarrhoea and clinical symptoms of deficiency of this vitamin [26].

Haematopoietic elements

Vitamin B_{12}, FA and iron (Fe) supplementation are considered for the prevention and treatment of anaemia. The WHO, MSF and UNICEF recommend a single dose of 5 mg FA orally on the day of admission. Iron supplementation is recommended only during the rehabilitation phase due to iron toxicity, which in

[1] Guidelines from countries in sub-Saharan Africa, Central Asia and Southern Asia.

malnourished patients may increase oxidative stress, contribute to electrolyte imbalance, disrupt metabolic processes and worsen intestinal infections. Only after correction of critical abnormalities (about 2 weeks), it is recommended to supplement Fe in children > 6 months (3 mg of elemental Fe/kg in 2 divided doses) [48]. Only 2 of 14 international guidelines and 2 of 23 national guidelines recommended similar supplementation in children < 6 months [17]. One national guideline recommended supplementation double dose of elemental iron in malnourished infants. In other guidelines, the recommendation was either not provided or nutritional treatment with the F-100 formula was considered sufficient [17]. Although many studies have shown equal and sometimes significantly greater importance of vitamin B_{12} in preventing and treating anaemia in children with SAM, none of the guidelines recommend its supplementation [61-65].

Cautious feeding

Depending on the child's age, severity of malnutrition and associated diseases, nutritional treatment involves breastfeeding, formula F-75, formula F-100, diluted formula F-100 (F-100D), infant formula (IF), ready-to-use therapeutic food (RUTF), oral nutritional supplements (ONS), and home-made milk feeds. The first phase of treatment (up to 7 days) is extremely important due to the fact of a precisely calculated dose of food, which aims to avoid failure in the treatment of malnutrition and especially overnutrition, including in the form of re-feeding syndrome. Most guidelines are consistent as to the frequency and methods of feeding in the first phase of treatment. A child > 6 months of age should be fed orally using a teaspoon, cup or syringe. If the child is unable to swallow food on its own, it is rec-ommended to feed via nasogastric (NG) tube and to withdraw it as soon as the child is able to swallow. The guidelines are consistent as to the gradual feeding of the child with the appropriate calories. Muscle and tissue catabolism will increase when feeding < 80 kcal/kg/day, while feeding > 100 kcal/kg/day may contribute to a serious metabolic imbalance. The main complications of overnutrition and overhydration in the first phase of treatment are congestive heart failure and death. Most common errors are due to excessive volume of food given at one time, excessive sodium intake and high protein intake. International and national guidelines have well-described tables, thanks to which health care workers can easily calculate and monitor the amount of food administered [14-17, 26, 39, 48]. The problem begins in children with SAM < 6 months because many guidelines do not specify this group in their dietary recommendations. In 6 of 13 international guidelines this topic was omitted completely, in 7 of 13 it was recommended to continue breastfeeding without detailed information, and 6 of 13 guidelines recognised F-75, F-100, F-100D and IF as a substitute for breastfeeding and details of feeding were presented [17]. What the guidelines do not seem to take into account is the maternal peridelivery mortality in developing countries, which results in orphaned infants for whom no breastmilk is available due to the lack of breast milk banks.

In a double-blind randomised trial, F-100 and F-100D were found to be of high safety in children < 6 months. In addition, F-100 restored the nutritional status of children much more effectively and faster than IF [66]. Attempts have also been made to examine the transition from formula F-75 to RUTF according to WHO recommendations. It turned out that the transition in the first time was only possible in 65% of cases, and almost impossible in acutely malnourished children or those with severe illnesses [67]. Rytter et al showed a strong correlation between feeding milk-rice porridges to children with SAM and the occurrence of refeeding syndrome (even with moderately low plasma phosphate levels) and F-75 was considered a safer product [68].

Nevertheless, there are questions about the availability of these nutritional preparations, both ready-made offered by WHO/UNICEF and those prepared at hospital or home using the recipes provided in the WHO and UNICEF training materials. In both cases, there are often problems with the distribution of food products or individual ingredients to create a standardised nutrient. This is often deepened by social unrest, corruption and a lack of financial support for treatment facilities in developing countries. Furthermore, compared to alternative nutritional approaches, RUTF improves recovery and slightly increases the rate of weight gain. Unfortunately, the effect on malnutrition recurrence or mortality after going on a normal diet is not fully known. The authors recommend further randomised controlled trials [69].

Conclusion

The lack of consistency between international and national guidelines on nutrition of children with SAM makes it difficult to treat malnourishment in developing countries and most understatements occur in the treatment of infants < 6 months old. This topic requires many research trials that will significantly help tosolve the problem of diagnosis and pharmacological-nutritional treatment of children 0-59 months.

It is necessary to unify the NSA and the rules of admitting children for nutritional treatment in medical facilities, because underdiagnosis may end in unnecessary death. In addition, specialised expert groups studying the problem of malnutrition should attempt to present new treatments that could be used in the field internationally. The experience of local medical personnel who care for the malnourished should also be taken into account. It is also worth asking the question why there is the problem of so many differences in treatment protocols, and why there is so little scientific research in places affected by poverty. If almost 1/3 of children under 5 are malnourished in Africa, this fact should motivate to create professional and reliable standards of treatment child with SAM in developing countries.

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RESEARCH ARTICLE

Sex-related differences in patients undergoing radiofrequency ablation of atrioventricular nodal reentrant tachycardia

Joanna Sokołowska[1], Magdalena Sokołowska[2], Jakub Adamowicz[2], Dorota Zyśko[3], Jadwiga Radziejewska[4], Agnieszka Sławuta[5]

[1]Praxis Joanna Sokołowska, Ingolstadt, Germany
[2]Department of Cardiology, Kłodzko County Hospital, Kłodzko, Poland
[3]Department of Emergency Medicine, Wrocław Medical University, Wrocław, Poland
[4]Kłodzko County Hospital, Kłodzko, Poland
[5]Department of Internal and Occupational Diseases, Hypertension and Clinical Oncology, Wrocław Medical University, Wrocław, Poland

Abstract

Background: Atrioventricular nodal reentry tachycardia (AVNRT) is the most common paroxysmal supraventricular tachycardia. The relatively ineffective antiarrhythmic drugs and the predominant young age makes the catheter ablation the therapy of choice in many patients. This results in predominance of this arrhythmia in electrophysiological labs. The aim of the study was to analyze the gender-related differences among patients undergoing the radiofrequency catheter ablation of slow pathway entrance to the atrioventricular node. **Material and methods:** The study group comprised of 147 consecutive patients with diagnosed atrioventricular nodal reentry tachycardia, who underwent the radiofrequency catheter ablation (RFCA) of slow pathway. Patients have been divided into 2 groups, based on sex. **Results:** The overall 97.3% of effectiveness of RFCA was observed. Women were significantly younger than men (53.7 +/- 17.2 vs. 57.7 +/- 9.8 years) with lower radiation dose (2383.5 +/- 1993.2 vs. 2891.6 +/- 2377.1 cGyxcm2). **Conclusions:** Younger age of women in comparison to men during RFCA of AVNRT reflects earlier onset of symptoms in women. Gender does not affect the time of fluoroscopy, but the higher rate of inducible tachycardia after RFCA in women may suggest the existence of anatomical difficulties or the operator's apprehensions. Sex-related difference in radiation dose that we have observed may result from the greater volume of the men's chest.

Keywords: AVNRT · RF ablation · age · gender

Citation

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Corresponding author:
Agnieszka Sławuta, Department of Internal and Occupational Diseases, Hypertension and Clinical Oncology, Wrocław Medical University, Wrocław, Poland
e-mail: aslawuta@tlen.pl
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Introduction

Atrioventricular nodal reentry tachycardia (AVNRT) is the most common type of paroxysmal supraventricular tachycardia, accounting for approximately 60% of all narrow-QRS-complex tachycardias [1-2]. AVNRT is up to 4 times more likely to affect women than men and tends to appear in young patients (mean age of 32 years) [2-4]. The reentrant mechanism of this arrhythmia results from the existence of the 'fast' and 'slow' atrioventricular nodal entry pathways, differing in conduction velocity and refractory period [5]. Due to the relatively ineffective antiarrhythmic pharmacotherapy and the predominant young age of the patients, catheter ablation continues to be considered the treatment of choice [6]. This method was introduced in 1982 by Gallagher et al [7]. The slow pathway ablation is a highly-effective method, with a success-rate of over 91-95%, minor recurrence index and a very low complication rate of 0.2-0.7% [8-9].

The recommended invasive treatment resulted in AVNRT being one of the dominant clinical entities treated in electrophysiology labs and could influence the change in the patient population. The prevalence of this arrhythmia also contributed to better training of the physicians performing the ablation procedures. Moreover, the newly available techniques, such as cryoablation, could change the electrophysiologists' attitude toward the endpoints of the first ablation, in particular in younger patients. We further hypothesize that the patient's characteristics and effective results assessment have changed along with an increased number of performed ablation procedures.

Aim

The aim of the study was to analyze the gender-related differences among patients undergoing the radiofrequency catheter ablation (RFCA) of slow pathway entrance to the atrioventricular node.

Materials and methods

The study group comprised of 147 consecutive patients with diagnosed atrioventricular nodal reentry tachycardia, who underwent the RFCA of slow pathway between January 2012 and December 2017. Standard RFCA was performed using one diagnostic decapolar deflectable catheter located in the coronary sinus. We used 4 mm tip, non-irrigated, radiofrequency catheters for His-bundle location and the procedure itself. The temperatures were initially set for 52° Celsius (C) and then increased to 56-58° C. The RF ablation was preceded by an electrophysiological study aiming at the assessment of the properties of the atrioventricular junction and implicitly at the induction of the AVNRT. The procedure was performed in the presence of dual atrial echoes during programmed atrial pacing on patients with a clinically confirmed arrhythmia, after excluding an accessory pathway. The ablation process was aimed to change the electrophysiological properties of the slow pathway eventually to total elimination of the slow pathway conduction. Clinically, the purpose of the procedure was the non-inducibility of the arrhythmia or profound changes to the AV junction properties which could prevent the tachycardia recurrence.

Patients were divided into 2 groups based on sex. Parameters, such as age, cycle length duration, Wenckebach point, time of fluoroscopy, the radiation exposure and effect of the procedure were analyzed. The effect of the procedure was rated based on the scale presented in the table 1. The analyzed parameters are presented as the means and standard deviations. Assessment of the statistical significance was performed using the non-parametric Mann-Whitney U Test. P value < 0.05 was considered statistically significant.

Table 1. Assessment of the radiofrequency catheter ablation of slow pathway entrance to the atrioventricular node procedure efficacy

Score	Effect
0	Ineffective procedure
1	Slight slow pathway modification, single echo beats
2	Impossible to induce arrhythmia
3	Deep slow pathway modification, the presence of AH 'jump' in AV conduction
4	Periodic occurrence of a AH 'jump' in AV conduction
5	Absence of the conduction in a slow pathway

AV – atrioventricular

Results

The clinical and procedural characteristics of the studied patients were presented in table 2.

In 4 cases - all female patients the non-inducibility of the tachycardia could not be obtained; there was no such case among men. The overall 97,3% of effectiveness was observed. Women were significantly younger than men (53,7 +/- 17,2 vs. 57,7 +/- 9,8) with lower radiation dose (2383,5 +/- 1993,2 vs. 2891,6 +/- 2377,1). We did not observe any statistically significant sex-related differences among the patients within the other parameters.

Suenari et al. women were also significantly younger than men [16]. The above-mentioned study by Liuba et al. showed however the differences in age of patients with heart disease and with lone AVNRT.

Associated heart disease was present in patients who experienced the first episode of tachycardia at a significantly older age (women 50 +/- 18 and men 45 +/- 20) what more precisely reflects the features of our population [14]. The differences in AV conduction properties are probably the reason of different incidence of AVNRT [16]. In women Wenckebach block point was lower than in men. The same results presented Liu et al. in study on sex differences in AV conduction [17].

Table 2. The analyzed parameters in the patient sample

	Women (n = 104)	Men (n = 43)	All patients (n = 147)	P value
Age (years)	53.7 ± 17.2	57.7 ± 9.8	55.2 ± 14.9	p < 0.05
Cycle length (ms)	381.2 ± 74	377.2 ± 58.3	380.3 ± 70.4	n.s
Wenckebach point (ms)	377.1 ± 78.3	389.4 ± 80.9	390.5 ± 79.5	n.s
Fluoroscopy (s)	335.5 ± 229.2	338.3 ± 187.4	336.3 ± 217.2	n.s
Radiation dose (cGy x cm2)	2383.5 ± 1993.2	2891.6 ± 2377.1	2532.2 ± 2117.1	p < 0.05
Effect of the procedure (scale)	3.0 ± 1.3	3.2 ± 1.0	3.1 ± 1.2	n.s

Discussion

RFCA is a highly successful method in both men, and women. According to the literature, women experience more symptoms than men, but they have longer time of delay before ablation [10-11]. Carnlöf et al. showed, that 17% of women stated that they were not taken seriously (vs. 7% men) and were misdiagnosed more frequently as suffering from panic disorders [12-13]. According to the results of Liuba et al. acute success rate and the recurrence rate were similar in both sexes, although some authors claim that women are more likely have certain arrhythmia symptoms after the procedure [14]. In our study, women undergoing RFCA were younger than men, what can be explained by the earlier onset of symptoms in women. This association was documented by Deneke et al. with onset of symptomatic AVNRT at age of 38 +/- 18 in women vs. 51 +/- 18 years in men (p = 0.01) [15]. In the study

The duration of fluoroscopy did not differ between sexes, but there was a difference in radiation exposure between men and women. Those results are similar to earlier studies and most probably should be attributed to the patients' body dimensions and the default settings of fluoroscopy [10, 16, 18].

Conclusions

Younger age of women in comparison to men during RFCA of AVNRT reflects earlier onset of symptoms in women. Sex does not affect the time of fluoroscopy, but the higher rate of inducible tachycardia after RFCA in women may suggest the existence of anatomical difficulties or the operator's apprehensions. Sex-related difference in radiation dose that we have observed may result from the greater volume of the men's chest.

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RESEARCH ARTICLE

Can medical staff have visible tattoos? A survey study among students

Anna Paprocka-Lipińska[1], Alan Majeranowski[1], Małgorzata Drozd-Garbacewicz[1], Małgorzata Mazanek[2], Maria Hebdzińska[2], Joanna Styszko[2]

[1]Department of Ethics, Medical University of Gdańsk, Poland
[2]Students Circle of Bioethics, Department of Ethics, Medical University of Gdańsk,Poland

Abstract

Background: Tattoo is becoming a more and more common form of body decoration of people from representatives of various professions.The aim of this study was: what is the opinion of university students about medical staff having visible tattoos. **Material and methods:** The study was conducted among the students of four universities in Gdańsk. The questionnaire contained questions about the acceptance of visible tattoos in people working in medical professions. The respondents were also asked about their attitudes to tattoos as a form of body decoration and whether they had tattoos themselves. The statistical analysis was performed using IBM SPSS Statistics 25 software. **Results:** Filled-in questionnaires were obtained from 676 respondents, including 477 students of the medical university and 199 students of non-medical universities. The students who have tattoos themselves accept visible tattoos in healthcare professionals to a significantly greater extent (92%) than those who do not have tattoos, but the acceptance of visible tattoos in healthcare professionals in this group turned out to be very high too (75%). The respondents most readily accepted a visible tattoo on the skin of a laboratory diagnostician (75%). **Conclusions:** University students, regardless of their university profile, consider a visible tattoo as a completely acceptable phenomenon in healthcare professionals.

Keywords: health care professionals · visible tattoos · dress code

Citation

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Corresponding author:
Anna Paprocka-Lipińska, Department of Ethics, Medical University of Gdańsk, Poland
e-mail: anna.paprocka-lipinska@gumed.edu.pl

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Introduction

Tattoo, defined as intentional and permanent skin pigmentation, is becoming a more and more common phenomenon in the public space. According to an epidemiological study from 2015, the incidence of tattoos among the inhabitants of industrialised countries which indicate that approximately 30% of the adult population has at least one tattoo [1]. While in the past tattoos were mainly a form of expression of belonging to a subculture or social group, today they have become a vivid form of body decoration. Recently, having a tattoo has become a common phenomenon in various social groups and professions, including healthcare.

Aim

The aim of the study was to find out what is the opinion of university students about people working in medical professions having visible tattoos that cannot be easily covered with clothes (on the face, neck and hands).

Material and methods

A survey was conducted among the students of four universities in Gdańsk: the Medical University of Gdańsk, Stanislaw Moniuszko Academy of Music in Gdańsk, Gdańsk University of Technology and the University of Gdańsk. The self-administered questionnaire consisted of questions about the acceptance of medical professionals having visible tattoos. The respondents were also asked about their attitudes to tattoos as a form of body decoration and whether they had tattoos themselves. The study was approved by the Independent Bioethics Committee for Scientific Research of the Medical University of Gdańsk (approval no. NKBBN/724/2018-2019).

The statistical analysis was performed using IBM SPSS Statistics 25 software. The data was analysed using statistical description and comparison of subgroup results with chi-square test (comparison of proportions). The assumed probability value was $p < 0.05$, which means that the differences between the compared groups were considered as statistically significant if the p-value was smaller than 0.05.

Results

A completed questionnaires were obtained from 676 respondents, including 477 students of the medical university and 199 students of the non-medical universities. The majority of them were women: 77% among the medical university respondents and 83% among the non-medical university respondents.

In total, 21% of the respondents confirmed having a tattoo. Majority of them were women (23% vs. men 12%) from the non-medical universities (31% vs. medical university 17%).

Surprisingly, 64% of the students responded affirmatively to the question whether medical staff should follow some kind of a dress code. The affirmative responses were significantly more common among the students of the medical university than among the non-medical students from the (67% vs. 55%, $p < 0.05$). The analysis of the responses to the question "do you find tattoos an attractive form of body decoration?" shows that 69% of the respondents consider this form of body decoration as attractive, with affirmative responses significantly more frequent among the students of the non-medical universities (75% vs. 66%, $p < 0.05$). A statistically significant difference was observed also between the male and female respondents. Female students answered the question affirmatively more often than males (71% vs. 60%, $p < 0.05$). The negative answer to this question was chosen by 16% of the respondents, significantly more frequently by the medical university students (19%) than by those studying at the non-medical universities (9%, $p < 0.05$).

Asked about their acceptance of healthcare professionals having visible tattoos, 79% of the respondents answered affirmatively. The affirmative answer was chosen significantly more often by the non-medical university students (84% vs. 76% for the medical university students, $p < 0.05$).

The data about the acceptance of particular medical professionals having visible tattoos is presented in Table 1. According to our study participants, visible tattoos are the most acceptable on laboratory diagnosticians, followed by nurses, dentists and physicians. The students were most reluctant to accept clinical psychologists with visible tattoos.

The respondents who have tattoos themselves were more reluctant to express limitations for the external appearance of healthcare professionals while the respondents who do not have tattoos were more restrictive in the topic (51% vs. 67% for limitations in the external appearance, which is statistically significant, $p < 0.05$). Similarly, the students who have tattoos themselves accept visible tattoos in healthcare professionals to a significantly greater extent (92%) than those who do not have tattoos ($p < 0.05$). However, the acceptance of visible tattoos in healthcare professionals in the latter group also turns out to be quite high (75%).

Table 1. Responses to the question "in your opinion, can healthcare professionals listed below have visible tattoos?"

	NO	It does not matter	YES
Clinical psychologist	16.9%	19.8%	63.3%
Physican	14.8%	19.8%	65.4%
Nurse	14.6%	19.1%	66.3%
Dentist	13.5%	18.8%	67.8%
Paramedic	10.1%	19.2%	70.7%
Physical therapist	8.6%	19.4%	72.0%
Pharmacist	8.4%	20.3%	71.3%
Dietician	5.2%	22.2%	72.6%
Laboratory diagnostician	3.4%	21.2%	75.4%

Discussion

Tattoo, that is intentional permanent skin pigmentation using exogenous substances, dates back to about 3,000 years BC, and became popular in Western Europe after the travellers' expeditions of the 17th century [2]. In the past, tattoo had (and probably may still have) significant symbolic meaning in certain social groups (e.g. prisoners or the lower class) [3]. Recently, tattooing has become increasingly popular, fashionable and a form of artistic expression. According to the estimations, approximately 20-30% of adults from the industrialised countries of the Western Europe have at least one tattoo [4]. In our study, the fact of having a tattoo was confirmed by 31% of students from the non-medical universities and 17% of students from the medical university, which corresponds with literature data, for example with the paper by Rogowska et al. about the level of knowledge about tattoo-related complications in university students in the Tricity agglomeration [5].

Numerous scientific publications have attempted to answer the questions why such a great (and still increasing) number of people of various educational and professional backgrounds decides on permanent, invasive skin pigmentation and what are the possible consequences of it. Kluger et al. lists 6 categories of motivations for having a tattoo, indicating that two of them (tattoos as a form of body decoration and to emphasize one's individualism) are most common in adults [1]. Similar motivations are indicated in a review article about tattoos in women and their health implications during pregnancy, labour and breastfeeding [4].

The increasing popularity of tattoos inspires also a reflection on how people with a visible tattoo are perceived by the society. Stuppy et al. concluded that a visible tattoo in a patient may be the cause of negative perception of this patient by medical staff and students of medicine [6]. Moreover, Ellis showed that stereotypical perceptions of people with tattoos still exist, which leads to some limitations, e.g. potential employers stated that having a visible tattoo may be the cause of a job candidate's rejection [7].

Other studies were devoted to the patients' perception of healthcare professionals with visible tattoos and piercings. The results of some earlier research clearly show that patients have negative attitudes, e.g. perceive nurses with tattoos as less professional and less competent [8]. Similar results have been obtained for physicians with nose or lip rings [9]. However, in a paper about the perception of the emergency room doctors Cohen et al. concluded that having a visible tattoo or piercing does not influence the perception of medical staff by emergency room patients [10]. The publication caused a heated debate in the Internet, which shows that a visible tattoo in people employed by the healthcare system seems to be fully acceptable by patients, and in some cases it may even be useful for starting the patient-doctor relationship [11-14].

An Scottish study conducted in 2018 showed that physicians with visible tattoos are perceived negatively both by medicine students and other physicians [15]. It was also noted that there are no provisions or regulations regarding the issue and that there is a need for discussion about the limitations in the expression of one's own individuality in medical professions.

The results of our study indicate high tolerance among both medical and non-medical university students for tattoos in healthcare professionals, regardless of what their own preferences are and whether they have tattoos themselves. It must be stressed that hitherto there are no limitations concerning the physical appearance of healthcare professionals, although there may be some local regulations in particular healthcare centres. The Polish Medical Ethics Code mentions only the need to represent the profession with dignity and that 'physicians cannot promote unhealthy

attitudes, also outside their professional work' [16]. As tattoo may be linked to a risk of infections or allergic reactions, having a visible tattoo may be questionable from this point of view.

Conclusions

1. Regardless of their field of study, university students consider it completely acceptable for healthcare professionals to have a visible tattoo, but they simultaneously state that such professionals should be subjected to some rules as to their physical appearance (dress code).
2. Medical university students seem slightly more conservative in their opinions about the limitations in the appearance of medical staff. However, their acceptance of visible tattoos on healthcare professionals is still high (although lower than of students of non-medical universities).
3. The students who do not like tattoos as a form of body decoration and do not have tattoos themselves, are still quite liberal when it comes to visual tattoos in healthcare professionals. However, they express their acceptance significantly less frequently than students who like tattoos or have a tattoo themselves.

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RESEARCH ARTICLE

Awareness of the role of cardiovascular risk factors and their prevention – comparison between rural-urban and urban adolescents

Dawid Ostrówka[1,2], Tadeusz Dereziński[3], Maria Nowak[4], Anna Komand[1], Marta Jancewicz[1], Anna Szyndler[1], Jacek Wolf[1], Krzysztof Narkiewicz[1]

[1]Department of Hypertension and Diabetology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; Center of Translational Medicine, Medical University of Gdańsk, Gdańsk, Poland
[2]Department of Pediatrics, Heamatology and Oncology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland
[3]NZOZ Esculap, Gniewkowo, Poland
[4]First Department of Cardiology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

Abstract

Background: Unhealthy habits (poor diet, smoking and hazardous alcohol drinking) often originate from early-life. We assessed the knowledge on selected cardiovascular and cancer risk factors, healthy habits and its implementation among adolescents and the correlation with their place of residence. **Materials and methods:** A survey-based study (38-item inventory) was conducted among adolescents from urban and rural-urban areas recruited in two Tricity high-schools and one junior high school from Gniewkowo, respectively. **Results:** A total of 410 students (59% girls) from Tricity and 287 (51% girls) from Gniewkowo completed the inventory. The mean age was 15.3 years. Students from Gniewkowo spend weekly 8.9 ± 6.2 hours on structured physical activity, which contrasts with 5.5 ± 4.5hrs in Tricity ($P < 0.001$). Gniewkowo residents restrained from alcohol consumption in 38.7% vs. 31.1% in Tricity ($P = 0.04$); were active smokers at 9.4% vs. 4.2% ($P = 0.007$); regular fruits and vegetables consumption was low in both Gniewkowo and Tricity 11.8% vs. 8.6% ($P = 0.19$); respectively. The awareness of the risk factors of non-communicable diseases was more common amongst Tricity adolescents. This was consistently coupled with the knowledge on preventive methods. **Conclusions:** The level of knowledge on common non-communicable disease risk factors is higher among teenagers from urban areas, however this does not necessarily translate to more frequent introduction of healthy lifestyle.

Keywords: CVD risk factors · adolescents · smoking · physical activity

Citation

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Corresponding author:
Anna Szyndler, Department of Hypertension and Diabetology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; Center of Translational Medicine, Medical University of Gdańsk, Gdańsk, Poland
e-mail: anna.szyndler@gumed.edu.pl
No external funds.
Available online: www.ejtcm.gumed.edu.pl

Introduction

Most of the chronic non-communicable diseases and unhealthy habits of the middle- and older-age, such as obesity, hypertension, smoking, excessive salt intake and alcohol consumption originate from childhood and adolescence. Of more, there is a compelling body of evidence showing that the classical environmental risk factors (primarily recognized in adulthood) negatively determine cardiovascular (CV) risk in early life-time. This generally holds true to insufficient level of education about healthy habits along with its implementation into daily life (e.g. physical activity, diet or body weight control). Evidently, body weight excess constitutes the most important single contributing factor to childhood hypertension [1-2]. This is of particular importance as the prevalence of obesity has considerably increased among children during the recent decades [3-4]. Today it is clear that the obesity epidemic will translate to shorter life span of todays' generation as compared to their parents' [5-6].

Additionally, novel risk factors emerged recently such as the growing popularity of e-cigarettes among adolescents. This may have a detrimental impact on recently recorded favorable trends in smoking cessation records. Smoking in the childhood is a recognized and very potent risk factor for continued smoking in adulthood [7-8].

Given that cardiovascular diseases are a leading cause of premature death, effective preventive methods should be implemented as early as possible. Adolescents should be aware of different ways of reducing CV risk which need to be implemented on every day basis.

Therefore, we aimed to assess the awareness of CV risk factors, the knowledge about CV preventive measures, and the true lifestyle habits in two groups of adolescents recruited from urban and rural-urban areas of Poland (i.e. the Tricity and town of Gniewkowo).

Materials and methods

In the years 2016-2017 groups of junior-high (from the rural-urban area of Gniewkowo, 8 thousand inhabitants) and high school students (Tricity agglomeration, ~1 million inhabitants) were enrolled into the study. All students volunteered to participate in the study. Those who did not consent or their parents/legal guardians did not provide an informed consent were not included in the survey (Attachment 1). During their school hours, the participants anonymously answered the 38-item questionnaire (questions adopted after Ostrówka D. et al.) [9]. The questionnaire composed of two main domains related to the awareness of risk factors (1) and the self-reported lifestyle habits such as physical activity, dietary approach, and substance use (2). The section regarding attitudes and practices included multiple-choice as well as open questions. Basic anthropometric and medical family history data was also collected i.e. weight, height, as well as their parents' CVD history. The anthropometric data was matched with Polish adolescent-specific percentile charts. The collected data was tabulated in MS Excel and analyzed with standard statistical package (Statistica 10, Statsoft, Poland). Chi-square test and student's t-test were used to assess the statistical significance for the comparison between two groups. P-value < 0.05 was considered statistically significant.

Results

A total of 697 students were enrolled into the study; 410 from urban area schools (243, 59.3% were girls) and in 287 from rural-urban area (146, 50.9% were girls). The mean age of the surveyed students was 15.3 years (14.3 ± 0.9 years in Gniewkowo, 16.4 ± 0.5 years in Gdańsk; $P < 0.001$). Based on self-reported weight and height, the students' BMI were assessed and matched with Polish adolescent-specific percentile charts [10] (Figure 2).

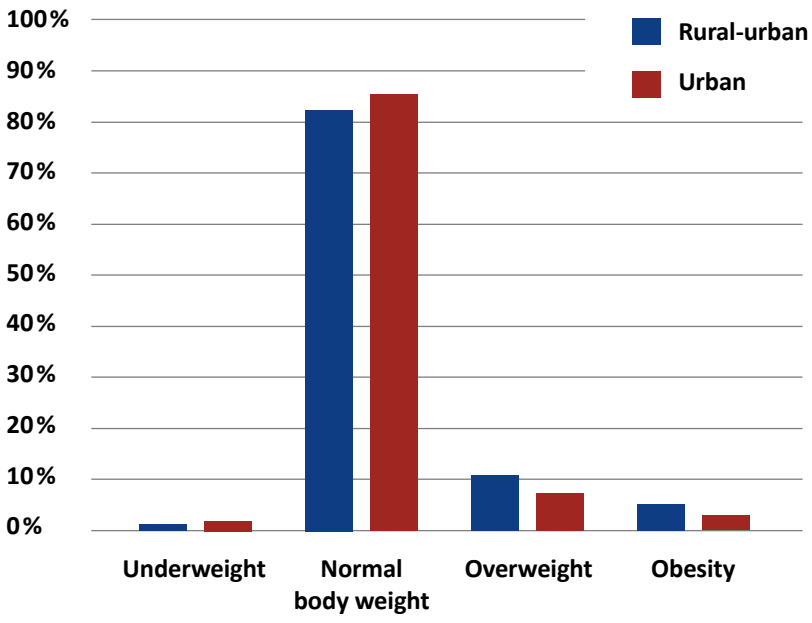


Figure 2. Comparison of BMI among our rural-urban and urban respondents

Physical activity

Awareness of the positive role of regular physical activity in the prevention of cardiovascular disease was significantly lower in the rural-urban population. The results of our study show that in both groups approximately 7 out of 10 students participate in out-of-school physical activities in urban and rural-urban areas; this was comparable in both studied groups. Additionally, no differences between the rural-urban and urban area students were noted with respect to number of sport activities (Table 1). Rural-urban adolescents, however, claim to spend more time on physical activity, on both daily (1.99 ± 1.24 h vs. 1.39 ± 1.00 h) and weekly basis (8.86 ± 6.17h vs 5.5h ± 4.5h) as compared to their peers from the urban area. At the same time the percentage of students, who declared spending 2 or more hours and 4 or more hours in front of TV set or computer was comparable between groups.

Smoking and psychoactive substances

Approximately, one-third of the rural-urban area students have already started tobacco smoking in their early years whereas in the urban agglomeration this phenomenon was less common and noted among 20% of our respondents (P = 0.002). The age of rural-urban students, who smoked their first-ever cigarette was significantly lower than among the urban students (12.0 ± 2.8 yrs vs. 14.6 ± 1.4 yrs; P < 0.001). Twice as many adolescents in the rural-urban area declared active smoking as in the urban area (9.4% vs. 4.2%; P < 0.01). Furthermore, the rural-urban students who used tobacco regularly tended to smoke over 3 times more cigarettes per day than their smoking urban peers (Table 2).

Tobacco usage was also more prevalent among the parents of the rural-urban adolescents: 56.6% of students have at least one smoking parent, in comparison to urban parents where only 23.7% of them smoke on daily basis. Therefore, the percentage of students exposed to passive smoking in rural-urban area is twice as high as in the urban agglomeration (Table 2).

Urban students identified tobacco usage as a possible cause of cancer and lung diseases more frequently than their rural-urban peers. Only two thirds of students in both groups associated smoking cigarettes with CVD, and less than half of the students, irrespective of their place of residence, identified smoking as a risk factor of stroke (Table 2).

Table 1. Attitude towards sport and sedentary lifestyle among our rural-ubran and urban respondents

	Rural-urban	Urban	P-value
Percentage of students involved in out of school physical activities ≥ 1/week	70.0%	73.4%	0.34
Average time spent daily on physical activity (h)	1.99 ± 1.24	1.39 ± 1.00	< 0.001
Average time spent weekly on physical activity (h)	8.86 ± 6.17	5.5 ± 4.5	< 0.001
Students participating in 3 or more types of sport disciplines	8.7%	10.0%	0.79
Students using computer or TV set for 2 or more hours per day	48.6%	47.2%	0.76
Students using computer or TV set for 4 or more hours per day	13.6%	14.0%	0.91
Students who consider regular physical activity as a CVD protective measure	86.0%	97.1%	< 0.001

Table 2. Awareness of the role of smoking and excessive alcohol consumption in the development of cardiovascular disease

	Rural-urban	Urban	P-value
Alcohol and recreational drugs related data			
Students who never drank alcohol	38.7%	31.1%	0.04
Students who consider excessive alcohol consumption to cause hypertension	67.4%	67.7%	0.93
Students who tried drugs in the past	13.4%	13.2%	1
Students who witnessed drugs use	29.7%	43.6%	< 0.001
Smoking-related data			
Students who tried smoking in the past	31.0%	21.1%	0.002
Average age of smoking initiation [years]	12.0 ± 2.8	14. 6± 1.4	< 0.001
Proportion of current smokers	9.4%	4.2%	0.007
Average number of cigarettes smoked per day	10.4	3.4	< 0.001
Current smokers' years of smoking [years]	3.4	2.6	0.33
Current smokers with at least one parent smoking	81.4%	47.1%	0.02
Non-smoking students who have at least one parent smoking	53.7%	22.6%	< 0.001
Students informed by health professionals about negative effects of smoking	34.7%	43.3%	0.03
Students who consider smoking to cause			
cancer	85.0%	98.0%	< 0.001
heart diseases	79.1%	82.4%	0.28
stroke	45.6%	39.9%	0.14
lung diseases	91.9%	98.5%	< 0.001
hypertension	64.7%	64.8%	0.98
Students who consider reduction of smoking and alcohol consumption to decrease risk of CVD	73.9%	91.2%	< 0.001

A different trend was observed in terms of alcohol use in between the studied groups. Rural-urban students more often indicated that they have never drank alcohol in their life. Whereas the number of students who experimented with illicit psychoactive substances was comparable in both of the studied groups with up to 15% more rural-urban adolescents reporting eye--witnessed drug use.

Dietary habits

The number of students, who declare to eat 5 or more portions of fruits and vegetables per day, is low in both groups. Only around half of the studied populations reports eating low-fat diet on a regular basis, and portion of adolescents, who eat fast food is almost 2 times higher in the urban area. Detailed comparisons are summarized in Table 3.

Knowledge of CVD risk factors

The awareness of CVD risk factors was lower in the rural-urban area group. The percentage of correct answers to all the questions in this domain was lower by 10-20% among those students. An exception is the question about regular fruit and vegetable consumption – the answers were almost the same in both groups ($P > 0.05$) (Table 4).

Table 3. Dietary habits of our rural-urban and urban respondents

	Rural-urban	Urban	P-value
Students who eat ≥ 5 portions of fruit or vegetables/day	11.8%	8.6%	0.19
Students who eat fast food ≥ 1/week	26.2%	44.8%	< 0.001
Students who declare to reduce fat in their diet	59.5%	55.5%	0.30
Students who add salt to their meals	42.3%	35.1%	0.56

Table 4. The awareness of and applying CVD risk-reducing activities into daily life

	Students who consider the following activities to reduce risk of CVD			Students who regularly apply the following activity in their daily life		
	Rural--urban	Urban	P-value	Rural--urban	Urban	P--value
Body weight reduction	73.9%	93.9%	< 0.001	77.1%	81.1%	0.21
Regular physical activity	86.0%	97.1%	< 0.001	72.5%	68.6%	0.27
Limiting smoking and alcohol consumption	73.9%	91.2%	< 0.001	84.6%	91.1%	0.01
Reducing salt amount in meals	66.2%	82.3%	< 0.001	61.8%	61.7%	1
Regular fruit and vegetable consumption	80.5%	83.1%	0.42	80.4%	87.3%	0.02
Fat reduction in meals	66.8%	86.2%	< 0.001	59.5%	55.5%	0.31

Table 5. The percentage of students correctly identifying diseases that are a consequence of HT

	Rural-urban	Urban	P-value
Stroke	34.0%	46.2%	0.002
Myocardial infarction	70.2%	92.4%	< 0.01
Kidney diseases	31.7%	28.0%	0.31
Lower limb artherosclerosis	52.0%	73.7%	< 0.001

The following pattern was also observed in the responses to the questions about the causes and consequences of arterial hypertension. Adolescents from the rural-urban area less frequently associated target organ damage with HT. Yet, both groups rarely associated kidney diseases and stroke with hypertension (Table 5).

Discussion

In our study the rural-urban adolescents dedicated considerably more time both daily and weekly to out-of-school physical activities and concurrently these junior-high school students were significantly more likely to smoke than urban high-school students. Disturbingly, the age of smoking initiation among adolescents in urban-rural area is approximately 2 years earlier in comparison to students dwelling in the bigger cities. Both groups of surveyed teenagers accurately identified unhealthy diet, smoking and excessive alcohol consumption with incident of the commonest cardiovascular consequences. Interestingly, this association is poor with respect to cerebrovascular consequences. Knowledge about risky health behaviors as well as causes and consequences of hypertension is significantly better among urban youngsters, however no significant difference was observed in terms of regular pro-healthy behaviors in the studied populations.

Physical activity

Physical activity is considered one of the crucial elements of a healthy lifestyle. The World Health Organization (WHO) recommends adolescents to engage in physical exercise for at least 60 minutes every day in order to preserve health [11]. The health benefits following that routine are well-established [12-13].

However, recent meta-analysis including 34 countries shows that only 23% of boys and 15% of girls meet these WHO criteria [14-15]. This trend is reflected in the Polish population, where only around one in five adolescents declares moderate to vigorous physical activity (at least 60 minutes of exercise for 7 days/week) [16]. In contrast, both of the groups we studied appear to meet the above criteria. Nonetheless, a distinct discrepancy is observed - both daily and weekly exercise were significantly higher in rural-urban group. The following trend was reflected in HBSC 2014 study, where factors such as place of residence – namely rural-urban area favored physical activity [17]. This trend can be explained by several factors. Greater presence of shopping centers and cinemas in urban areas creates opportunities for passive leisure activities. For instance, in 2016 8-16% of students from two major Polish cities of Kraków and Katowice declared to visit a shopping center on a daily basis [18]. It is also important to mention, that limited access to sport facilities, such as swimming pools or stadiums, in rural-urban areas did not facilitate participating in sport activities by studied adolescents. Still, many participants reported being active in local parks, playgrounds. Another important issue differentiating both groups may be a way of commuting to school. In rural-urban areas school is often easily accessible on foot or by bike. In contrast, studies show that as many as 40% of students in urban area are driven to school by their parents and one in five rides public transportation [19].

Smoking

Tobacco smoking is an important CVD risk factor, responsible for short term consequences such as shortness of breath, higher resting heart rate, biochemical

blood changes – increased LDL level and higher insulin resistance, which in adulthood evolves to atherosclerosis [20], stroke [21] or myocardial infarction [22].

Over the past decade the positive trend in smoking cessation was observed in both the pediatric [23] and adult populations [24]. However, the prevalence of smoking in adolescents is still high. An American questionnaire-based study assessed that percentage of students who smoke cigarettes in junior-high and in high school is 2.2% and 8%, respectively (7.2% and 20.2% for any tobacco products) [25]. In the EU the percentage of adolescents (13-17 years of age) who declare active smoking is even higher, with some studies reporting up to 30.9% of active smokers [26]. A questionnaire-based study, conducted in semi-urban district of Istambul among 11-14 year olds describes the prevalence of smoking at least once in the participant's lifetime at the level of 12% and the rate of current smoking as 3.6% [27]. At the same time the HBSC 2014 study in Polish population reports the percentage of students who smoke on daily basis or at least once a week at the level of 9% in urban and 7.7% in rural-urban area [17].

Our results do not fully support this data. The number of current smokers among the surveyed adolescents in the rural-urban area is twice as high as corresponding number in urban area. Additionally, adolescents in the rural-urban environment are at higher risk of long term consequences, such as COPD or lung cancer development, as they tend to smoke 3 times more cigarettes a day, than their peers in Tricity, which is coupled with their greater exposure to passive smoking.

We also observed significantly more adolescents in rural-urban group who tried smoking at least once in their life. Studies show that of those individuals who have tried smoking, about one-third become daily smokers [28]. More importantly, tobacco usage is extremely addictive among adolescents [29]. Moreover, early onset of smoking appears to entail social consequences, such as lower educational attainment in life and low socio-economic status [28].

Additionally disturbing is the high number of smokers among the parents of our rural-urban respondents. Students from families with at least one parent smoking, self-report smoking more frequently. More importantly, there are over twice as many rural-urban adolescents, who restrain themselves from smoking and at the same time are exposed to tobacco smoke by their parents as in the urban group. Similar situation was reported by Kaleta et al. with almost 40% of Polish adolescents being exposed to involuntary smoking at home [30]. At the same time it was established that parental tobacco usage poses as a risk factor for adolescents smoking initiation [31].

Adolescents in rural-urban area report being less frequently informed by their doctor about negative consequences of smoking. In turn we observe early smoking initiation, higher percentage of first ever smokers, longer smoking history despite being 2 years younger than their urban peers. Sadly, in both groups less than half of studied population identified tobacco use as stroke risk factor.

What should also be mentioned is that approximately two in three rural-urban and urban adolescents alike, drank alcohol at least once in their life. Our results stand in opposition to several studies which suggest that alcohol drinking habit has greater frequency in rural areas [32-33]. Furthermore, the percentage of rural-urban students, who declared abstinence was higher than in the urban area. It is important to note that our urban respondents were on average 2 years older than their rural-urban peers. Nonetheless, one should be aware that early initiation in alcohol use is connected with greater use in adulthood.

Dietary habits

The WHO recommendations state that prevailing good health is supported by 400g (5 portions) of fruit and vegetables per day. Several studies support the beneficial role of such diet in decreasing the risk of CVD [34], diabetes [35], stroke [36] and cancer [37]. What appears to be of a great concern is fact that dietary habits formed in childhood tend to be continued later in adulthood. Therefore, only 1 out of 10 of respondents in both studied groups reporting regular fruit and vegetable consumption is unsatisfactory.

Knowledge of CVD risk factors

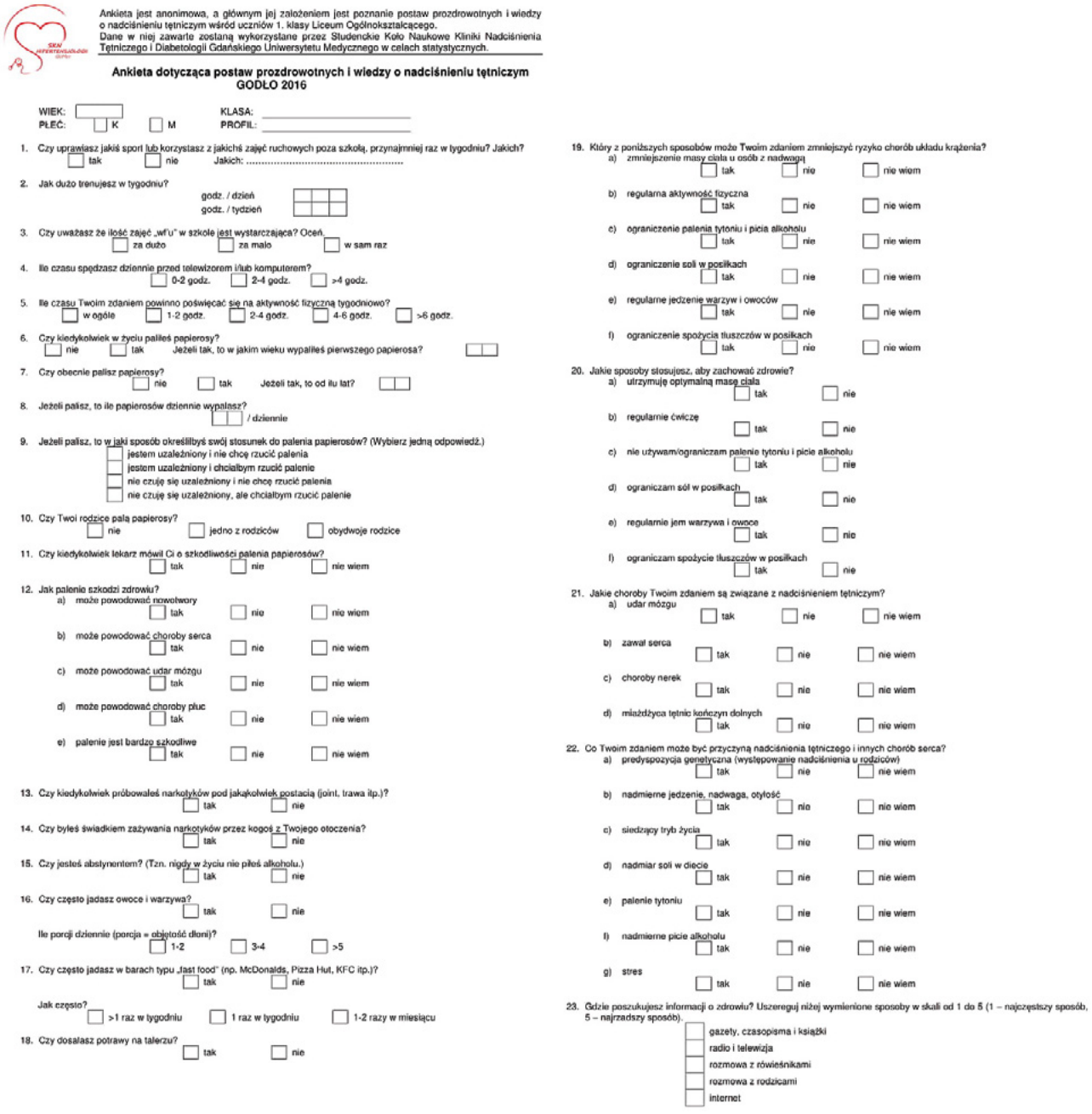
Knowledge of CVD risks factors and preventive measures was generally higher among the urban adolescents, who as mentioned earlier were on average 2 years older than their rural-urban peers. With this in mind our study showed that the greater level of knowledge on CVD risk factors did not clearly correlate with a healthier lifestyle. It remains the matter of a debate whether reported differences may have a potential to modify future CVD incidence. Swedish researchers observed that knowledge of CVD risk factors, such as smoking, had no effect on future use [38]. The following tendency is also visible in our study, where greater knowledge level did not clearly correlate with a healthier lifestyle. The following observation was also demonstrated in CARDIA study, where in the group of young adults knowledge on risk factors itself did not predict a 10-year change in CVD risk factors intensity (marginal impact on reducing obesity rates) [39].

Despite the lack of direct evidence of the influence of risk factors awareness among adolescents, on the development of CVD in adulthood, it should be mentioned that it may potentially lower the probability of CVD in long term.

Conclusion

In general, rural-urban and urban students have sufficient theoretical background on the role of healthy lifestyle to effectively prevent cardiac diseases in adulthood. However, the surveyed teenagers are rarely aware of the link between hypertension, and smoking to cerebrovascular consequences such as stroke. The latter may have a substantial impact on smoking patterns, particularly among the rural-urban students, which is an area for intensifying the education and introduction of all other preventive measures. Although, the level of knowledge on CVD risk factors is higher among teenage students from urban areas, this does not necessarily translate to a healthier lifestyle.

Attachment 1. Survey questionnaire adapted from Ostrówka D et al. [9]

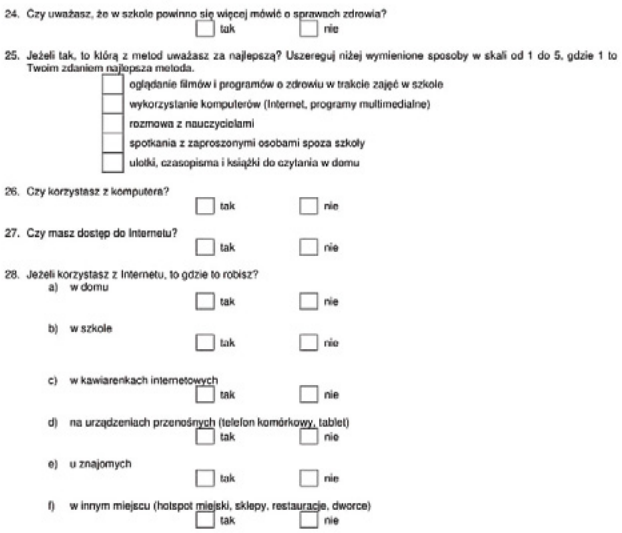


Ankieta jest anonimowa, a głównym jej założeniem jest poznanie postaw prozdrowotnych i wiedzy o nadciśnieniu tętniczym wśród uczniów 1. klasy Liceum Ogólnokształcącego.
Dane w niej zawarte zostaną wykorzystane przez Studenckie Koło Naukowe Kliniki Nadciśnienia Tętniczego i Diabetologii Gdańskiego Uniwersytetu Medycznego w celach statystycznych.

Ankieta dotycząca postaw prozdrowotnych i wiedzy o nadciśnieniu tętniczym GODŁO 2016

WIEK: ☐☐ KLASA: _____
PŁEĆ: ☐ K ☐ M PROFIL: _____

1. Czy uprawiasz jakiś sport lub korzystasz z jakichś zajęć ruchowych poza szkołą, przynajmniej raz w tygodniu? Jakich?
☐ tak ☐ nie Jakich: .....
2. Jak dużo trenujesz w tygodniu?
godz. / dzień ☐☐
godz. / tydzień ☐☐☐
3. Czy uważasz że ilość zajęć „wf'u" w szkole jest wystarczająca? Oceń.
☐ za dużo ☐ za mało ☐ w sam raz
4. Ile czasu spędzasz dziennie przed telewizorem i/lub komputerem?
☐ 0-2 godz. ☐ 2-4 godz. ☐ >4 godz.
5. Ile czasu Twoim zdaniem powinno poświęcać się na aktywność fizyczną tygodniowo?
☐ w ogóle ☐ 1-2 godz. ☐ 2-4 godz. ☐ 4-6 godz. ☐ >6 godz.
6. Czy kiedykolwiek w życiu paliłeś papierosy?
☐ nie ☐ tak Jeżeli tak, to w jakim wieku wypaliłeś pierwszego papierosa? ☐☐
7. Czy obecnie palisz papierosy?
☐ nie ☐ tak Jeżeli tak, to od ilu lat? ☐☐
8. Jeżeli palisz, to ile papierosów dziennie wypalasz?
☐☐ / dziennie
9. Jeżeli palisz, to w jaki sposób określiłbyś swój stosunek do palenia papierosów? (Wybierz jedną odpowiedź.)
☐ jestem uzależniony i nie chcę rzucić palenia
☐ jestem uzależniony i chciałbym rzucić palenie
☐ nie czuję się uzależniony i nie chcę rzucić palenia
☐ nie czuję się uzależniony, ale chciałbym rzucić palenie
10. Czy Twoi rodzice palą papierosy?
☐ nie ☐ jedno z rodziców ☐ obydwoje rodzice
11. Czy kiedykolwiek lekarz mówił Ci o szkodliwości palenia papierosów?
☐ tak ☐ nie ☐ nie wiem
12. Jak palenie szkodzi zdrowiu?
a) może powodować nowotwory ☐ tak ☐ nie ☐ nie wiem
b) może powodować choroby serca ☐ tak ☐ nie ☐ nie wiem
c) może powodować udar mózgu ☐ tak ☐ nie ☐ nie wiem
d) może powodować choroby płuc ☐ tak ☐ nie ☐ nie wiem
e) palenie jest bardzo szkodliwe ☐ tak ☐ nie ☐ nie wiem
13. Czy kiedykolwiek próbowałeś narkotyków pod jakąkolwiek postacią (joint, trawa itp.)?
☐ tak ☐ nie
14. Czy byłeś świadkiem zażywania narkotyków przez kogoś z Twojego otoczenia?
☐ tak ☐ nie
15. Czy jesteś abstynentem? (Tzn. nigdy w życiu nie piłeś alkoholu.)
☐ tak ☐ nie
16. Czy często jadasz owoce i warzywa?
☐ tak ☐ nie
Ile porcji dziennie (porcja = objętość dłoni)?
☐ 1-2 ☐ 3-4 ☐ >5
17. Czy często jadasz w barach typu „fast food" (np. McDonalds, Pizza Hut, KFC itp.)?
☐ tak ☐ nie
Jak często?
☐ >1 raz w tygodniu ☐ 1 raz w tygodniu ☐ 1-2 razy w miesiącu
18. Czy dosalasz potrawy na talerzu?
☐ tak ☐ nie
19. Który z poniższych sposobów może Twoim zdaniem zmniejszyć ryzyko chorób układu krążenia?
a) zmniejszenie masy ciała u osób z nadwagą ☐ tak ☐ nie ☐ nie wiem
b) regularna aktywność fizyczna ☐ tak ☐ nie ☐ nie wiem
c) ograniczenie palenia tytoniu i picia alkoholu ☐ tak ☐ nie ☐ nie wiem
d) ograniczenie soli w posiłkach ☐ tak ☐ nie ☐ nie wiem
e) regularne jedzenie warzyw i owoców ☐ tak ☐ nie ☐ nie wiem
f) ograniczenie spożycia tłuszczów w posiłkach ☐ tak ☐ nie ☐ nie wiem
20. Jakie sposoby stosujesz, aby zachować zdrowie?
a) utrzymuję optymalną masę ciała ☐ tak ☐ nie
b) regularnie ćwiczę ☐ tak ☐ nie
c) nie używam/ograniczam palenie tytoniu i picie alkoholu ☐ tak ☐ nie
d) ograniczam sól w posiłkach ☐ tak ☐ nie
e) regularnie jem warzywa i owoce ☐ tak ☐ nie
f) ograniczam spożycie tłuszczów w posiłkach ☐ tak ☐ nie
21. Jakie choroby Twoim zdaniem są związane z nadciśnieniem tętniczym?
a) udar mózgu ☐ tak ☐ nie ☐ nie wiem
b) zawał serca ☐ tak ☐ nie ☐ nie wiem
c) choroby nerek ☐ tak ☐ nie ☐ nie wiem
d) miażdżyca tętnic kończyn dolnych ☐ tak ☐ nie ☐ nie wiem
22. Co Twoim zdaniem może być przyczyną nadciśnienia tętniczego i innych chorób serca?
a) predyspozycja genetyczna (występowanie nadciśnienia u rodziców) ☐ tak ☐ nie ☐ nie wiem
b) nadmierne jedzenie, nadwaga, otyłość ☐ tak ☐ nie ☐ nie wiem
c) siedzący tryb życia ☐ tak ☐ nie ☐ nie wiem
d) nadmiar soli w diecie ☐ tak ☐ nie ☐ nie wiem
e) palenie tytoniu ☐ tak ☐ nie ☐ nie wiem
f) nadmierne picie alkoholu ☐ tak ☐ nie ☐ nie wiem
g) stres ☐ tak ☐ nie ☐ nie wiem
23. Gdzie poszukujesz informacji o zdrowiu? Uszereguj niżej wymienione sposoby w skali od 1 do 5 (1 – najczęstszy sposób, 5 – najrzadszy sposób).
☐ gazety, czasopisma i książki
☐ radio i telewizja
☐ rozmowa z rówieśnikami
☐ rozmowa z rodzicami
☐ internet



24. Czy uważasz, że w szkole powinno się więcej mówić o sprawach zdrowia?
☐ tak ☐ nie

25. Jeżeli tak, to którą z metod uważasz za najlepszą? Uszereguj niżej wymienione sposoby w skali od 1 do 5, gdzie 1 to Twoim zdaniem najlepsza metoda.
☐ oglądanie filmów i programów o zdrowiu w trakcie zajęć w szkole
☐ wykorzystanie komputerów (Internet, programy multimedialne)
☐ rozmowa z nauczycielami
☐ spotkania z zaproszonymi osobami spoza szkoły
☐ ulotki, czasopisma i książki do czytania w domu

26. Czy korzystasz z komputera?
☐ tak ☐ nie

27. Czy masz dostęp do Internetu?
☐ tak ☐ nie

28. Jeżeli korzystasz z Internetu, to gdzie to robisz?
a) w domu ☐ tak ☐ nie
b) w szkole ☐ tak ☐ nie
c) w kawiarenkach internetowych ☐ tak ☐ nie
d) na urządzeniach przenośnych (telefon komórkowy, tablet) ☐ tak ☐ nie
e) u znajomych ☐ tak ☐ nie
f) w innym miejscu (hotspot miejski, sklepy, restauracje, dworce) ☐ tak ☐ nie

29. Czy uważasz, że Internet może być dla Ciebie istotnym źródłem informacji dotyczących zdrowia?
☐ tak ☐ nie ☐ nie wiem

30. Ile masz wzrostu?
☐☐☐ cm

31. Ile ważysz?
☐☐☐ kg

32. Czy uważasz, że masz nadwagę?
☐ tak ☐ nie ☐ nie wiem

33. Ile powinieneś ważyć?
☐☐☐ kg

34. Jakie masz ciśnienie tętnicze?
☐ nie znam swojego ciśnienia
☐ moje ciśnienie to ☐☐☐ / ☐☐☐ mmHg

35. Jaka jest Twoim zdaniem norma ciśnienia tętniczego?
norma ciśnienia ☐☐☐ / ☐☐☐ mmHg

36. Czy chorujesz na jakąś chorobę przewlekłą? Jaka to choroba?
☐ nie ☐ tak Jaką: .....

37. Czy któryś z Twoich rodziców:
a) choruje na nadciśnienie tętnicze?
☐ nie ☐ jedno z rodziców ☐ oboje z rodziców ☐ nie wiem
b) przebył zawał serca?
☐ nie ☐ jedno z rodziców ☐ oboje z rodziców ☐ nie wiem
c) przebył udar mózgu?
☐ nie ☐ jedno z rodziców ☐ oboje z rodziców ☐ nie wiem
d) choruje na cukrzycę?
☐ nie ☐ jedno z rodziców ☐ oboje z rodziców ☐ nie wiem
e) ma nadwagę?
☐ nie ☐ jedno z rodziców ☐ oboje z rodziców ☐ nie wiem

38. Czy ktoś w Twojej rodzinie zmarł „na serce" w młodym wieku (przed 55 r.ż.)?
☐ tak ☐ nie ☐ nie wiem

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RESEARCH ARTICLE

Interdisciplinary treatment of large adrenocortical carcinoma infiltrating inferior vena cava

Małgorzata Dobrzycka[1], Piotr Spychalski[1], Urszula Rusek[2], Michał Brzeziński[2], Jarosław Kobiela[1], Przemysław Kłosowski[3], Monika Berendt-Obołończyk[3], Andrzej Łachiński[1], Krzysztof Sworczak[3], Zbigniew Śledziński[1]

[1]Department of General, Endocrine and Transplant Surgery, Medical University of Gdańsk, Poland
[2]Department of General Surgery, Students Scientific Circle, Medical University of Gdańsk, Poland
[3]Department of Endocrinology and Internal Diseases, Medical University of Gdańsk, Poland

Abstract

Background: Adrenal tumors are common neoplasms and majority of them are small, benign, hormonally inactiveadrenocortical adenomas. Whereas adrenal cancer is a rarely occurring (5% of adrenal tumors) but highly aggressive neoplasm. The early diagnosis and complete surgical resection is the only effective treatment option. Laparoscopic adrenalectomy is the gold standard for small and medium tumors. Whereas for large tumors classic adrenalectomy is considered a procedure of choice with a proven better oncological outcome. **Material and methods:** There were 245 patients with adrenal tumors operated in the Department of General, Endocrine and Transplant Surgery, Medical University of Gdańsk, Poland between 2014and 2018. **Results:** Out of entire series, there was one case of a 57-year-old female diagnosed with a large, advanced left adrenal tumor with invasion of vena cava. It was diagnosed in computer tomography and proven in core biopsy. Open adrenalectomy with thoracotomy was conducted to completely resect the tumor by the interdisciplinary team. **Conclusions:** In case of large adrenal tumour with vessel infiltration, a successful R0 resection can be performed by multi-specialist approach. For adrenal cancer early diagnosis based on the clinical, biochemical and imaging features and successful surgical treatment is crucial in significant prolongation of patient survival.

Keywords: surgical treatment · adrenocortical carcinoma · adrenal cancer

Citation

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Corresponding author:
Małgorzata Dobrzycka, Department of General, Endocrine and Transplant Surgery, Medical University of Gdańsk, Poland
e-mail: malgorzata.dobrzycka@gumed.edu.pl

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Introduction

Adrenocortical cancer (ACC) is a rare malignancy. The incidence is estimated to be 1 to 2 per million per year [1]. There is a predilection for the female sex with 2.5-fold higher prevalence [1]. Despite its rare occurrence, According is especially noteworthy due to its aggressive nature. The prognosis of ACC is poor with a 5-year overall survival rates below 30% in most series [2]. In addition, lymph node and/or distant organ metastases are already present in about 60% of patients at the time of diagnosis [3]. Early diagnosis of hormone-secreting adrenocortical tumor depends on the occurrence of clinical symptoms of excess of adrenocortical hormones. Whereas the diagnosis of non-secreting tumors is usually accidental in patients due to non-specific abdominal pain, nausea, vomiting and feeling of abdominal fullness [1-4].

The primary treatment of ACC is surgical excision [5]. Furthermore, chemotherapy with steroidogenesis inhibitors (especially mitotane) is crucial. The application of mitotane can be considered in adjuvant treatment and is the basis for the management of patients with diffused ACC. In the treatment of advanced disease, multi-drug chemotherapy is also used alone or in combination with mitotane. Currently, the basic treatment regimen is the combination of etoposide, doxorubicin and cisplatin (EDP) [1].

Series analysis

There were 245 patients with adrenal tumors operated in the Department of General, Endocrine and Transplant Surgery, Medical University of Gdańsk, Poland between 2014 and 2018. In 211 (86%) of them laparoscopic adrenalectomy was performed, whereas in 34 patients with large tumors classic adrenalectomy was performed. In histopathological examination there were 5 cases of ACC. In the presented case report, we describe the clinical picture of a patient with highly advanced, metastatic ACC. Furthermore, we present a highly specialized interdisciplinary approach towards patient care in case of a rare cancer.

Case report

A 57 year old woman (0.4%) was admitted to the Department of General, Endocrine and Transplant Surgery at the Medical University of Gdańsk (Poland) due to presence of a left adrenal tumor. The patient's history included autoimmune polyendocrine syndrome type 2 (APS2) diagnosed 10 years prior. Since then she received hormonal substitution for Hashimoto's disease and adrenal insufficiency (thyroxine, prednisone and fludrocortisone). Furthermore, she was diagnosed with hypertension one month before the admission to hospital. The patient's family history included her mother's death from adrenal cancer at the age of 69.

An outpatient abdominal ultrasound incidentally discovered a 97 x 75 x 94 mm tumor located in the left adrenal gland (near the superior pole of the left kidney). It had mixed echogenicity, peripheral and central flows, fluid spaces and fine calcifications. The diagnosis was confirmed in abdominal CT examination (Fig. 1). The lesion was 143 x 85 mm in transverse dimension and 98 mm (cephalocaudal dimension). In addition,

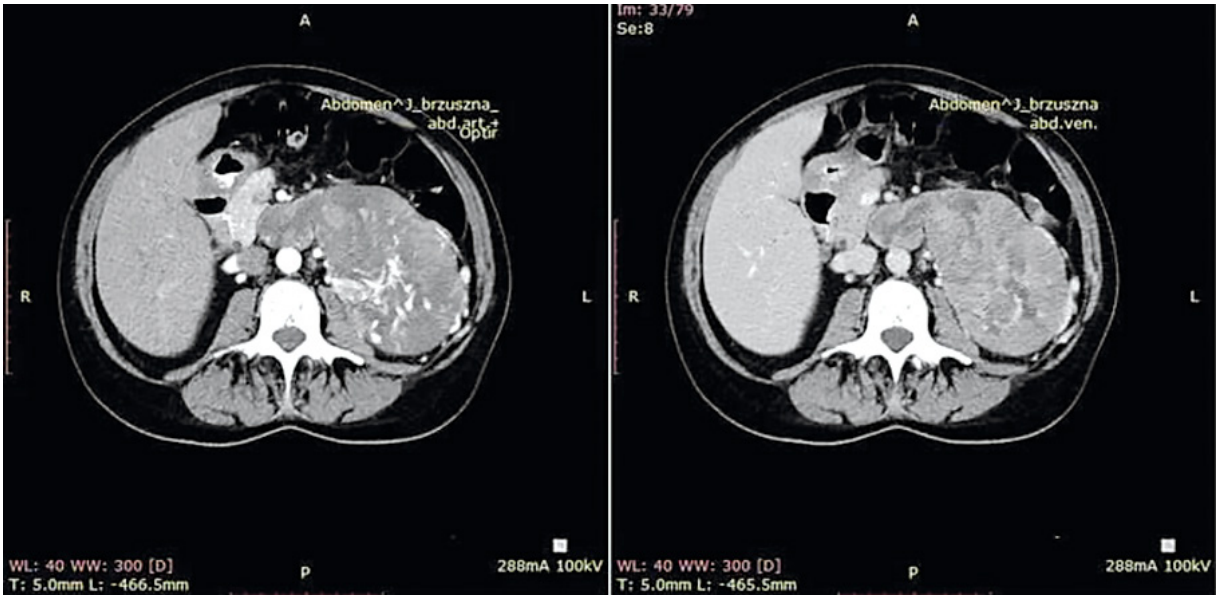

Figure 1. Abdomen CT. Left adrenal gland tumor. Infiltration of left renal vein, vena cava inferior and left kidney

Figure 2. Adrenal cancer resected en bloc with left kidney and vascular invasion to inferior vena cava

the CT images revealed infiltration and thrombosis of the left renal vein, ovarian vein and the inferior vena cava from the left renal vein inflow to the diaphragm level. Furthermore, a slight 5 mm hypodense focal lesion was identified in the liver segment IVa and a 4 mm nodule was revealed in the right lung segment 8 near the fissure. Endocrine diagnostics showed increased androgen concentration without any clinical symptoms of hyperandrogenism. The androstendione level was 29.7 ng/ml, (normal range 0.3-3.5 ng/ml), the dehydroepiandrosterone sulphate (DHEA-S) was also markedly elevated to 960 ug/dl, (normal range 26-200 ug/dl), the testosterone was elevated to 6.6 nmol/l (normal range 0.43-1.24 nmol/l) and the 17(OH)-progesterone was 7.7 ng/ml. The excretion of meta- and normetanephrine in a 24-hour collection of urine was normal. Loss of the circadian rhythm of cortisol secretion (morning cortisol level was 16 ug/dl and nighttime was 17 µg/dl) in this case was not very diagnostic because of adrenal insufficiency and hormonal substitution.

A core biopsy revealed the formation of a tumor originating from the adrenal cortex, with the following pathological characteristics: IHC:inhibin +/-, MelanA +, Ki67 7%, no signs of increased atypia, atypical divisions or necrosis. Together these features result in Weiss score > 3, indicating the malignant nature of the lesion. The patient was qualified for curative surgical treatment planned by an interdisciplinary team consisting of general and cardiac surgeons.

After the laparotomy, a 20 cm tumor displacing the kidney downwards was found in the left adrenal field. It was growing into the inferior vena cava through the left renal vein. Moreover, a solid 8mm lesion in the left lobe of the liver was exposed. No further signs of tumor spread were revealed. Then a right-sided thoracotomy was performed by a cardiac surgeon to obtain access to the inferior vena cava through the apex of the right atrium. Following this, IVC below the renal veins and the right renal vein were clamped. The tumor was extracted by incising the left renal vein at the entrance to the inferior vena cava. Later, the adrenal gland with the tumor, the left kidney, the retroperitoneal tissues and the spleen were resected en bloc (Fig 2). Next, a non-anatomical tumor resection of the left lobe of the liver with margins was performed. The surgery lasted 284 minutes. The estimated intraoperative blood loss was 1700 ml. Histopathological examination of the extracted tissue revealed ACC cells with atypical mitosis, hemorrhage and extensive necrosis (Fig 3). There was no evidence of invasion of the organ

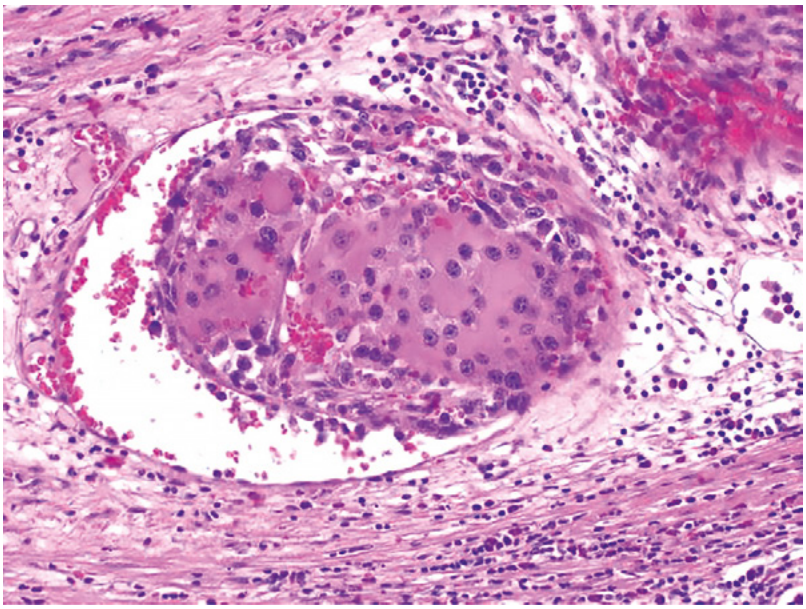

Figure 3. Microscopic intravascular invasion of adrenal cancer

capsule. Cancer was resected within the limits of the organ pouch. In addition, the tumor expanded into the renal vein. Metastasis was found in the removed liver tumor. The postoperative period was complicated by hematoma in right pleural cavity resulting from bleeding from the branch of right internal mammary artery and from the splenic artery stump (successfully treated with transarterial embolization). Hydrocortisone replacement therapy was conducted perioperatively. On postoperative day 15 the patient was discharged home. In laboratory follow-up 1 month after the surgery, the total testosterone and DHEA-S levels returned to normal (0.8 ng/ml and 15 ug/dl respectively). Later the patient was treated for metastasis found in CT with chemotherapy (mitotane, etoposide and cisplatin) and transarterial chemoembolization of the liver metastasis with lipiodol and doxorubicin.

Discussion

The diagnosis of adrenal mass should focus on distinguishing between benign and non-secreting masses from malignant or hormonally active lesions that require further treatment. It consists of a complete physical examination, biochemical evaluation of hormone secretion, and careful examination of radiological imaging tests. Adrenal tumor biopsy is contraindicated in the case of suspected ACC (due to the risk of local spread after damage to the tumor capsule) and pheochromocytoma (danger of hypertensive crisis). Its implementation is justified in the case of suspicion of metastases to the adrenal glands if imaging studies do not state clearly whether the lesion is benign or malignant and the unequivocal determination of the etiology of focal lesions will affect further therapeutic treatment. About 80% of the tumors are benign adenomas or adrenal tuberous hyperplasia. According to The European Network for the Study of Adrenal Tumors (ENSAT) classification, the patient described above was diagnosed with stage IV tumor with high grade malignant features in histological Weiss criteria [6-7].

The basic screening tests for hypercortisolism include test of inhibition of cortisol secretion after oral administration of 1 mg dexamethasone, daily excretion of free cortisol in the urine and a midnight salivary cortisol level. In women with adrenal tumors and with hyperandrogenisation syndrome, it is recommended to measure total testosterone, DHEA-S and 17(OH)-progesterone. High levels of testosterone (> 200 ng/dl), DHEA-S (> 800 µg/dl) and 17(OH)-progesterone are more often associated with ACC [8]. Our patient had an increased androgen concentration (total testosterone, 17(OH)-progesterone, androstendione and DHEA-S) and no circadian rhythm of cortisol secretion.

The coexistence of ACC with the history of APS2 might change the standard diagnostic process. In such cases, non-circadian secretion of cortisol should be considered because it is already disturbed as a result of APS2. Also, our patient's normal level of aldosterone seems intriguing. Before the tumor developed, the patient might have had reduced aldosterone levels due to the adrenal insufficiency, whereas secretion by the ACC brought this hormone to its normal level.

For localized ACC the only curative method is a complete resection (R0) of the tumor and it is considered as the treatment of choice. Superiority of open vs. laparoscopic adrenalectomy remains controversial. Laparoscopic adrenalectomy is the gold standard in adrenal tumors surgery but recent research has shown that open adrenalectomy is superior to laparoscopic approach in terms of disease-free survival and rate of 2-year disease-free survival, in spite of the larger maximum diameter of tumors and lesser benefit during the perioperative period [9-10]. Laparoscopic surgery is still not recommended in case of large tumor (>6cm) and if there is a suspicion of local invasion or the presence of metastases in regional lymph nodes. About 30-40% of patients are in the IV clinical stage at the time of diagnosis. The prognosis in these patients is significantly worse than in stage I and II, but with the predicted resectability R0 of the primary site and the resection of lung and liver metastases, they are still eligible for surgery. Due to the relatively frequent recurrences after treatment (range 19%-30% depending on the tumor stage), adjuvant therapy should be administered after the surgery [3]. It includes using mitotane and tumoral bed irradiation. In cases of oligometastatic disease, > 80% tumor mass resection and slow tumor progression, radiotherapy, radiofrequency ablation or transarterial chemoembolization with mitotane can be conducted [1].

Conclusion

In conclusion, the presented case has shown that in case of large, advanced ACC with vessel infiltration a successful R0 resection can be performed by multidisciplinary surgical team. For adrenal cancer early diagnosis based on the clinical, biochemical and imaging features and successful surgical treatment is crucial in order to achieve significant prolongation of patient survival.

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REVIEW ARTICLE

The usefulness and limitations of diffusion tensor imaging – a review study

Sara Kierońska[1,2], Paweł Słoniewski[2]

[1]Jan Biziel University Hospital Collegium Medicum Nicolaus Copernicus University,
Department of Neurosurgery and Neurology, Bydgoszcz, Poland
[2]Department of Neurosurgery, Medical University of Gdańsk, Poland

Abstract

Diffusion tensor tractography (DTI) has been used for planning of a brain pathology surgeries. Knowledge about the distances between neural tracts and brain tumours is believed to increase the patient safety and implies the extent of resection. The aim of the study was to demonstrate the contemporary possibilities and the clinical usefulness of DTI. Following the explanation of the technical basics of DTI, we presented the drawbacks and limitations of this visualisation technique. The most commonly outlined tracts are corticospinal tract (CST), arcuate fasciculus (AF) and frontal aslant tract (FAT). Tumour located in frontal, parietal or temporal lobe can affect the course of the CST. There are two basic possibilities to visualise CST: deterministic and probabilistic. The usefulness of DTI seems limited in imaging the neoplasms of either frontal or temporal region causing aphasia, which infiltrate the AF or the FAT. This limitation is probably related to divergent and patient-specific location of functional speech areas. Acquisition disturbances, ill-defined mathematical algorithms, surgery-related brain shift and defining wrong non-functional brain area are the sources of DTI inaccuracy, which is limiting its clinical application.

Keywords: Diffusion Tensor Imaging · tractography · corticospinal tract · arcuate fasciculus · frontal aslant tract

Citation

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Introduction

Tractography is a non-invasive method of visualizing the white matter of central nervous system (CNS) structures in vivo. It is possible to determine the direction and continuity of neural fibres in either CNS or peripheral nervous system by using diffusion tensor imaging (DTI), a specific sequence of magnetic resonance (MR) [1]. Tractography allows reconstructing the neural fibres in colourful projections that run simultaneously through particular anatomical regions of the brain. Important neural pathways are tracked

Corresponding author:
Sara Kierońska, Jan Biziel University Hospital Collegium Medicum Nicolaus Copernicus University, Department of Neurosurgery and Neurology, Bydgoszcz, Poland
e-mail: sara.kieronska@gmail.com
No external funds.
Available online: www.ejtcm.gumed.edu.pl

by utilising the connection map and their course correlates with some pathological changes in the CNS [2-3]. That information is essential in neurosurgeon's preoperative planning, as it leads to an improvement in setting boundaries for tumour resection and decrease of post-surgery neurological deficits.

Tractography utilises the data provided by the MR tensor, which returns information about size and the direction of the diffusion. The sketch of the white matter pathways through the selected anatomical points is based on the principles of voxel continuity [4]. There are several analytical methods used in the assessment of anatomical differences between specific groups of patients. Nevertheless, the most commonly used is the voxel-based analysis. It is easily adjustable to the needs of the neurosurgeon and makes it possible to assess the degree of tissue diffusion simultaneously throughout the encephalon, which points out the possible locations of tumour infiltrations. Another widely used method is an analysis of the region of interest (ROI) which enables the precise assessment of the degree of diffusion in hypothetically determined locations [5-6].

Studies conducted on neurosurgical patients revealed that total or subtotal brain tumor resection leads to improved survival. The specific success rate is directly connected with a lower risk of tumour relapse [7-8]. From the patient's perspective, it is crucial to maintain quality of life, motor function and speech after undergoing surgery [9]. The vast majority of available literature refers to the preclinical technical aspects of DTI and rarely describes its practical application. Currently, only several of these practical possibilities that DTI gives are utilised in modern neurosurgery. These need to be summarised in a comprehensive review, which is not only directed at neurosurgeons but also radiologists and neurologists. In this study, we reviewed not only the usefulness but also the potential limitations of DTI in brain tumour surgery.

Tractography

Tractography is a method of spatial imaging of computational radiological data. It allows various neural fibres to be tracked, which is a result of different diffusion of a single voxel. Many professional applications, both paid and freeware, are used for tracking, fusing of the sequences and comparative analyses. These are widely available and have great flexibility in the data processing. Images can be saved in a variety of formats, printed and transferred to operating rooms or used for research purposes. The most clinically valid and nonetheless spectacular graphic presentation of DTI is a directionally encoded colour (DEC) sequence. DEC is conditioned by the direction of the diffusion vector of white matter. According to built-in, automatic, anatomical atlases, applications allow precise determination of neural structures and some of the main fibre pathways. These structures are named regions of interest (ROIs). By setting one or more ROI, the application automatically calculates and draws white matter fibres. To note, visualising an individual neural pathway is also possible. The software also allows sketching the location of the tumour concerning the previously designated path.

At our department, we performed DTI for all patients with suspected tumour infiltration, according to internal DTI protocol, resulting in a total of 60 diffusion sampling directions acquired. Parameters of those MRI examinations were as follows:

- b-value: 1000 s/mm2,
- in-plane resolution: 1.95313 mm,
- thickness: 2 mm,
- angular threshold: 90°.

The obtained pattern of neaural tracts, as well as the outlined tumour, can be imported into the neuronavigation system, which seems to be the leading, practical advantage of all DTI methods.

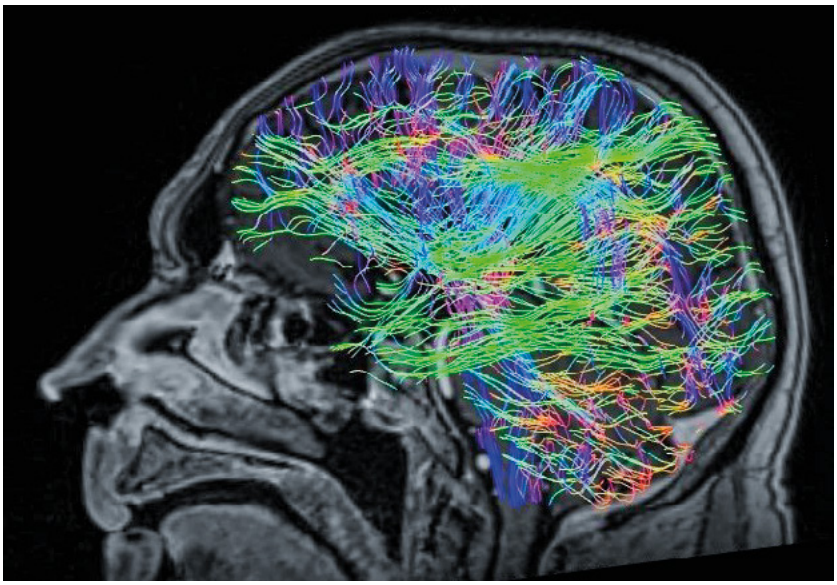

Figure 1. Directionally encoded colour (DEC) sequence of the diffusion tensor tractography depicts the course of white matter fibres. In standard markings, the red colour means left-right, green front-back and blue top-to-bottom directions of white matter fibres

There are two basic techniques for creating models of neural pathways: probabilistic and deterministic. The deterministic approach implies drawing the fibres in the system by marking one starting point and another ROI. Utilising this technique, the defined neural bundle assumes only one direction assigned to the single voxel. Therefore, the main limitation of this approach is the high anatomical variability of neural pathways and the fact that some of the fibres intersect each other [10]. Table 1 presents selected articles comparing both methods.

Table 1. Comparison of methods of tractography: the probabilistic and deterministic. The practical application of each technique was extracted from the studies

Author	Title	Year	Tract	Probabilistic vs. Deterministic	Clinical impact
Zolal A et al. [1]	Comparison of probabilistic and deterministic fibre tracking of cranial nerves	2017	Cranial nerves: II, III,V, VII,VIII	Probabilistic	Probabilistic tracking is more effective than the previously described deterministic
Schlaier JR et al. [2]	Probabilistic vs. deterministic fibre tracking and the influence of different seed regions to delineate cerebellar-thalamic fibers in deep brain stimulation	2017	Dentate-rubro thalamic tract	Probabilistic	Probabilistic fibre tracking was more sensitive and provides more accurate tracking solutions for dentate-rubro-thalamic tract
Jenabi M et al. [3]	Identification of the Corticobulbar Tracts of the Tongue and Face Using Deterministic and Probabilistic DTI Fibre Tracking in Patients with Brain Tumor	2015	Corticobulbar tract	Probabilistic	Probabilistic tractography successfully reconstructs the face- and tongue-associated corticobulbar tracts from the lateral primary motor cortex to the pons in both hemispheres
Jenabi M et al. [4]	Probabilistic fibre tracking of the language and motor white matter pathways of the supplementary motor area (SMA) in patients with brain tumors	2014	Broca's area to SMA	Probabilistic	The identification of unique areas of white matter according to the probabilistic method allows the location of the tract connecting Broca's area to SMA
Li Z et al. [5]	Diffusion tensor tractography of the arcuate fasciculus in patients with brain tumors: Comparison between deterministic and probabilistic models	2013	Arcuate fasciculus	Probabilistic	Probabilistic tractography reconstructs the arcuate fasciculus more completely and performs better through areas of tumor and/or edema

Burkett DJ et al. [6]	Deterministic Tractography of the Descending Tract of the Spinal Trigeminal Nerve Using Diffusion Tensor Imaging	2017	descending tract of the trigeminal nerve	Determinitsic	The identification of unique areas of white matter according to the probabilistic method allows the location of the tract connecting Broca's area to SMA
Anthofer JM et al. [7]	DTI-based deterministic fibre tracking of the medial forebrain bundle	2015	medial forebrain bundle	Determinitsic	Deterministic tractography with different ROIs provides variable delineations of the course of the medial forebrain bundle

Most authors use a probabilistic method for ascertaining a specific tract. The obtained images of DTI are easy to interpret for most of them [17-18]. The advantage of probabilistic tractography is an obtained sketch of neural tracts that presents any structural changes of white matter adjacent to pathological changes [18]. On the other hand, the deterministic method, is mostly used for the analysis of the course of fibres that have their ending in the voxels with the lowest FA value [10]. For the clinical purpose, the deterministic model is chosen less frequently, although it has some clinical advantages. In our experience, the deterministic approach results in better visualisation of the corticospinal tract (CST) adhering to tumours of the medial frontal lobe.

There are over 50 patients who had deterministic tracking of the CST before undergoing surgery at the Neurosurgery Department of the Medical University of Gdańsk (Poland). Those surgeries confirmed the position of CST with the clinical findings. Other studies confirm our observations [19].

Clinical application of tractography

The precise visualisation of the neural pathways and their topographic relation to the tumour increases the safety of the surgery, even though DTI fibres are not the same as the actual neural pathways [19-20]. Optimal preoperative planning allows the operating team to minimise the potential damage of vital white matter during the surgery [21-22]. The images created during the preoperative planning can be superimposed in realtime onto the view shown in the operative microscope. This way the neurosurgeon can remove the tumour relying solely on the preoperative planning in what is known as 'image-guided surgery' [23].

Corticospinal tract

The CST is the main neuronal route responsible for motor functions of the face, limbs and trunk. CST is composed of descending fibres starting in the pre-centre bend (4th Brodmann area) which transmits neural impulses through the pyramid up to the spinal cord [24]. Infiltration or destruction of CST caused by a brain tumour, ischemic stroke or subarachnoid haemorrhage affects the density of the fibres. Sterr et al demonstrated that the degree of the damage to the pyramidal pathway is closely related to subsequent motor deficits in patients after ischemic stroke [25]. The anatomy of the CST and its topography in relation to the tumour is essential when those two are close to each other [26]. Based on tractographic parameters, we can estimate the degree of CST injury and predict the postoperative neurological outcome [26]. The CST is the neural bundle most commonly tracked by neurosurgeons, including at our centre [27]. Various ROIs can be used to track CST, resulting in high variability rate. Weiss et al showed that an ROI set at the anterior inferior pontine region yielded better tracking results compared to the ROI set at the internal capsule [28-30]. Furthermore, CST was reconstructed from neural bundles passing through by cerebral peduncle, posterior limb of internal capsule and corona radiata in a patient after stroke [31]. This study confirmed the significance of a hind limb of the internal capsule as an ROI for CST

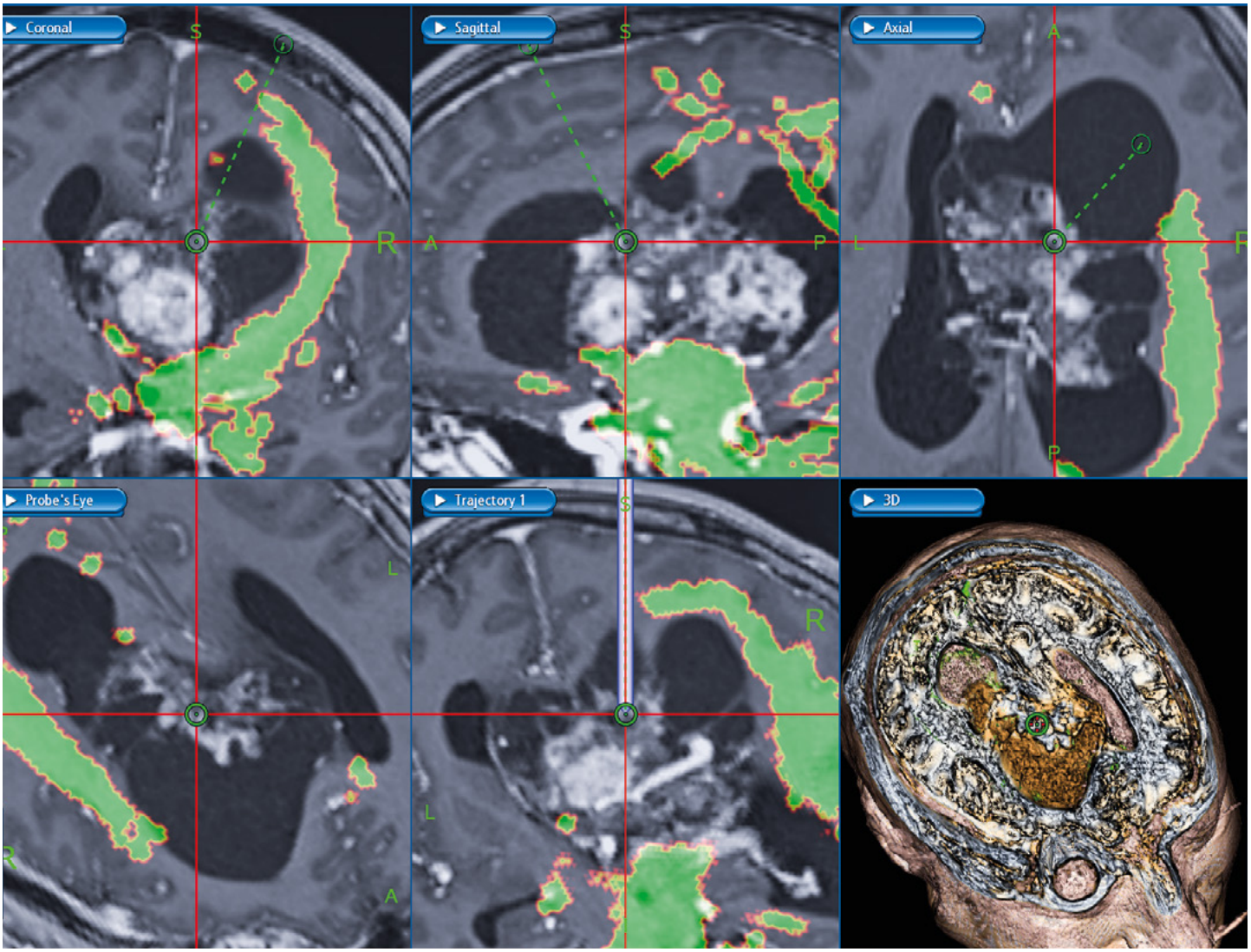

Figure 2. Planning of the surgical approach with the visualisation of the corticospinal tract of a patient with ventricular neurocytoma

tractography. Based on the above suggestions, our department has commenced the DTI analysis comparing the differences between CSTs with various ROIs. In our experience, we defined two main types of the anatomical ROIs (the cerebral peduncle and posterior limb of the internal capsule) and four additional endpoints: precentral gyrus, postcentral gyrus, supplementary motor area and frontal lobe.

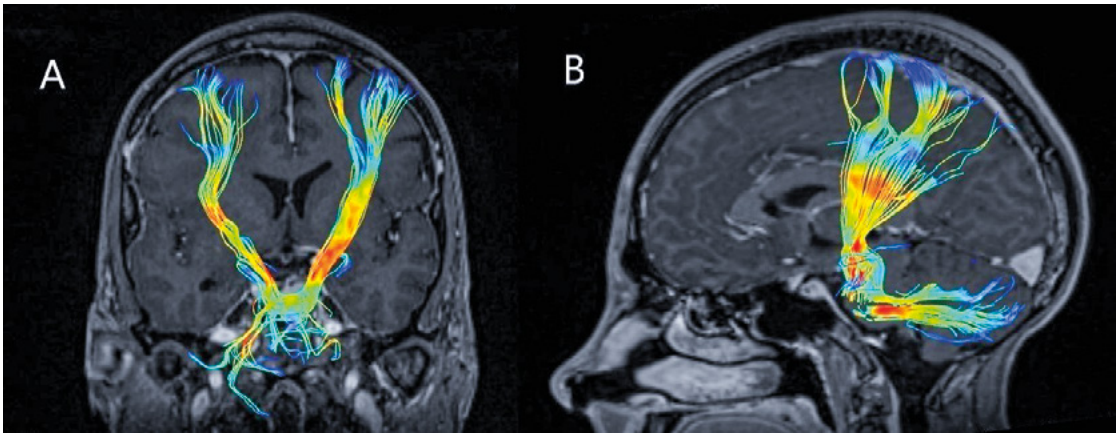

Figure 3. Corticospinal tract on preoperative tractography on coronal (A) and sagittal (B) planes

Arcuate Fasciculus (AF)

AF is the white matter pathway connecting the Broca speech centre (located in the frontal lobe) with the Wernicke speech centre (temporal lobe). CNS lesions infiltrating AF affect speech because the communication between the Broca and Wernicke areas becomes severed. The patient usually presents with so-called conduction aphasia [32-33]. DTI-based visualisation of AF is an widely accepted management for tumours of eloquent areas. The synchronisation of the tractography with the navigation system determines the precise location of the AF. Therefore, DTI sets boundaries for resection of a tumour located near AF and helps to prevent iatrogenic injury of the speech centre [34]. However, AF alone tractography could not always prevent postoperative aphasia. Cortical mapping, together with neurophysiological monitoring, could be applied for some more demanding tumours, although some surgeons prefer awake craniotomy [35]. Awake craniotomy also improves patient safety in terms of preserving speech functions [36]. The different location of both Broca and Wernicke area among individuals preclude the correct prediction of functionally active AF in DTI, what seems to be the main drawback of DTI tracking of AF, also confirmed by our experience.

Nevertheless, functional MRI also can unambiguously estimate the exact location of speech areas. Researchers should put more effort into studying DTI in terms of speech preservation as awake craniotomy resection is still more reliable in this case [37].

Frontal aslant tract

The frontal aslant tract (FAT), first described in DTI by Catani et al, contains neural fibres connecting the lower frontal bend (pars triangularis and pars opercularis of the operculum) with the supplementary motor area (SMA) and pre-SMA [38]. Tumors infiltrating SMA or pre-SMA may impede some motor functions, learning and aphasia. In a majority of patients, the FAT projected to the opercularis part of inferior frontal gyrus (IFG) and a greater number of fibres terminated at the triangularis part of IFG in left-handed patients [39]. The course of FAT through the inferior frontal lobe and the Broca's area suggests its significant role in the proper functioning of speech. Patients with progressive aphasia with a significant change within the FAT show particularly large changes in the correlation with AF [38-40]. In studies of the surgical treatment of patients with brain tumours, FAT lesions are associated with transient speech disorders and the occurrence of mutism and motor aphasia [34, 41]. The accurate prediction of the FAT location is possible thanks to the neuromonitoring techniques and direct stimulation of the cerebral cortex. In one study, the intraoperative stimulation of the left hemisphere FAT during craniotomy caused transient speech disorder of the stuttering type [34, 42].

In clinical practice, FAT could be determined to be a means of DTI in patients for whom an awake craniotomy is planned [43]. Baker et al. suggested that FAT and "crossed FAT" are of great importance for tumours infiltrating SMA and pre-SMA [37, 44].

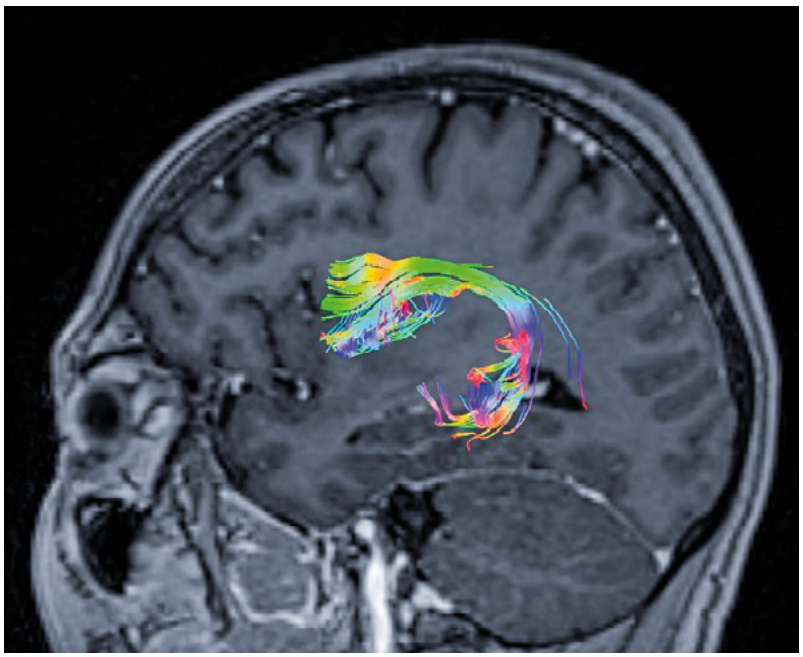

Figure 4. Arcuate Fasciculus connecting Broca's and Wernicke's areas

Limitations and future of tractograph

DTI is an imaging method used as a radiological tool for years. However, only the recent development of visualisation of neural tracts, tractography, makes it possible to use on personal computers. Frequent use of tractography leads to the constant improvement of reconstruction methods and these directly influenced the precision of treatment in the clinical setting. The correlation of DTI with a patient's neurological condition is sufficient for an adequate therapeutic process

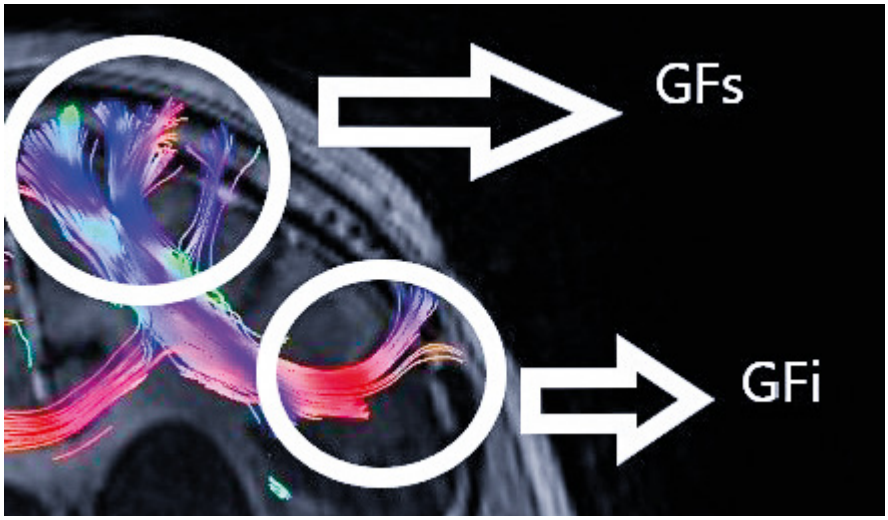

Figure 5. Frontal aslant tract based on two regions of interest--gyrus frontalis superior (GFs) and gyrus frontalis inferior (GFi). Abbreviations: GFs –gyrus frontalis superior, GFi – gyrus frontalis inferior

[45-47]. However, tractography is not considered as a standard approach due to its limitations, variability of obtained data and lack of standardisation of image acquisition parameters.

As mentioned earlier, tractography is a method of spatial imaging of computational radiological data and because of that use of DTI in surgical planning remains virtual. For patients with malignant tumours or significant brain edema, the identification of neural pathways is inaccurate [47]. Furthermore, in the case of sizable cerebrospinal fluid flow, there is a risk of motion artefacts occurring during the DTI acquisition. This functional limitation substantially affects the precision of tractography. For these reasons, DTI techniques should be regarded as complementary in surgical planning or as an educational tool [48].

On the other hand, DTI is still dynamically evolving. Thanks to its widespread use by neurosurgeons, we need continuous research to discover new clinical uses and possibilities of DTI. The main contemporary issue is to find the functional significance of each visualised neural tract. On the contrary, even if a particular amount of fibres is damaged during the surgery, it does not necessarily lead to noticeable neurological deficits [21]. It seems that the future of neural tract tracking lies in the development of a universal mathematical model for precise delineation of anatomic-functional structures [23].

Tractography, as a method of imaging, has been used for several years. We've been using it at out department since 2010. In most cases, acquisition parameters are the same but ways of determining the nerve path of our patients are based on the experience of the researcher currently responsible for the patient. Nevertheless, conclusions of all the researchers are in line with each other. Also other review articles coincide with our observations about the utility and reliability of the tractography as a standard diagnostic procedure. Furthermore, our results are in line with the experiences published by other teams about the necessity of using the tractography as an essential tool in treatment in patients with a brain tumour.

Conclusions

DTI is a clinically significant tool in the daily neurosurgical practice. In the current review, we provide examples where tractography is a valuable imaging adjunct. Owing to the limitations of DTI, combining tractography with intraoperative monitoring would allow more accurate preoperative planning and then increase the safety of the surgery. Further standardisation of DTI protocols is needed.

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REVIEW ARTICLE

Quality of life after laparoscopic sleeve gastrectomy – review of literature

Mateusz Wityk[1], Wojciech Makarewicz[2],

Cezary Kaczmarkiewicz[1], Maciej Bobowicz[2]

[1]Department of General and Oncological Surgery, Voivodeship Specialist Hospital of Janusz Korczak in Słupsk, Poland
[2]Department of Oncological Surgery, Medical University of Gdańsk, Poland

Abstract

Background: The last decade brought changes the most frequently performed types of bariatric procedures. Despite the well-documented positive impact of bariatric surgery on depression, somatic comorbidities, lifespan prolongation and cancer risk, there is still insufficient data on patients' quality of life (QoL) after this operation. **Methods:** PubMed and Scopus databases as well as Mendeley search engine were used to find publications from last ten years focusing on QoL after LSG. 702 abstracts were reviewed. 13 articles with 1630 patients in total were analyzed. **Results:** Six different QoL assessment tools were described in the reviewed literature: SF-36, BAROS, Moorehead-Ardelt II questionnaire, IWQOL-Lite, GIQLI and SF8. In majority of studies the QoL was improved. Pre- and postoperative assessment with SF-36 showed significant improvement. The mean BAROS score was 5.1-7.1 with 77-96% of patients achieving "good" to "excellent" outcomes. In some studies, QoL was better in females and in one study QoL was below the general population norms. Some studies demonstrated lack of improvement in QoL after LSG or no correlation between excess weight loss and health related QOL. **Conclusions:** High quality research about QoL after LSG is limited, though quality of life seems to be better after that procedure.

Keywords: bariatric surgery · metabolic surgery · BAROS · SF-36 · QoL

Citation

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Corresponding author:
Mateusz Wityk, Department of General and Oncological Surgery, Voivodeship Specialist Hospital of Janusz Korczak in Słupsk, Poland
e-mail: mateuszwityk@gmail.com

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Introduction

Obesity increases the risk of metabolic, cardiovascular and musculoskeletal diseases, depression and several types of cancer. In addition, obesity might lead to reduced quality of life, lower productivity and social disadvantages [1]. Obesity also decreases life expectancy [2]. The worldwide prevalence of overweight and obesity has doubled since 1980 to an extent that nearly a third of the world's population is currently classified as overweight or obese [3].

The superiority of surgery over conservative treatment for obesity and related diseases has been proven for many years [4]. Last decade brought changes in the trends of most frequently performed types of operations. A 2018 Worldwide Survey published by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) showed that the most frequently performed primary surgical bariatric/metabolic procedure in 2016 was laparoscopic sleeve gastrectomy (LSG) (53.6%), followed by Roux-en-Y gastric bypass (30.1%) and one-anastomosis gastric bypass (4.8%) [5].

The first sleeve gastrectomy was performed in 1988 as part of the biliopancreatic diversion with duodenal switch and since 2004 was accepted as a stand-alone bariatric procedure [6]. In the following years it became the most common type of surgical treatment of obesity in Poland (62%) and worldwide [5].

There are several measurable outcomes of bariatric surgery such as weight loss, resolution or improvement of comorbidities and an increase in life expectancy. One of the most important patient-reported outcomes, which is defining failure or success of bariatric surgery is Health-Related Quality of Life (HRQoL), however only few published studies focused on this end point [7-8]. There is some original research and literature reviews about QoL after bariatric surgery, comparing various methods of surgical technique [9]. Nevertheless, to our best knowledge, there are no reviews focusing directly on QoL after LSG and the relevant articles started to appear well after 2004 (2). In perspective of rising popularity of the LSG as the surgical treatment of choice for obesity, our aim was to assess the impact of this procedure on patients' quality of life (QoL).

Material & Methods

In 2010 LSG became the most frequently performed bariatric procedure in Poland, and thus our decision to include publications from the last 10 years [10]. We searched relevant publications that investigated adult participants (both sexes) who underwent LSG for obesity and underwent assessment of QoL at least once after 6-months of follow-up (or longer) with one of the well-established and validated tools for the QoL assessment (The 36-Item Short Form Health Survey (SF-36), Bariatric Analysis and Reporting Outcome System (BAROS) and it's updated version, The Moorehead-Ardelt Quality of Life Questionnaire (MA-II), The Impact of Weight on Quality of Life - Lite Questionnaire (IWQOL-Lite), The Gastrointestinal Quality of Life Index (GIQLI) and The 8-Item Short Form Health Survey (SF-8) [11-18]. We took into consideration all QoL outcomes depending on the design of the QoL form and the primary outcome was the change in the total score of the QoL assessment after LSG.

In this review we used PubMed and Scopus databases as well as Mendeley search engine for articles from last ten years focusing on quality of life after LSG. Search strategy was based on terms "sleeve gastrectomy" and "laparoscopy"/or "LSG" and "quality of life"/or "QoL" and was performed independently by two researchers (MW and MB). We excluded case reports, reviews, letters, duplicate studies, pediatric patients (< 18 years of age), studies with patient samples smaller than 50 patients (n < 50) and studies involving bariatric procedures other than LSG [e.g. laparoscopic Roux-en-Y gastric bypass (LRYGB), single-anastomosis gastric bypass (SAGB) or mini-gastric bypass (MGB), adjustable gastric banding (AGB)].

Results

Literature search

Initial search returned 702 abstracts (see Figure 1). Of those, 25 abstracts met the inclusion criteria. Full-texts of articles were obtained and reviewed. 12 articles were excluded for reasons such as analyzing the same groups of patients, using not validated QoL questionnaires or small patient samples (n < 50). We included 13 articles in the final analysis, with a total of 1630 patients and extracted the data (see Figure 1).

Patient Characteristics

In A total of 1630 adults underwent LSG as a treatment for morbid obesity. 1151 were female and 416 were male. BMI and age of patients are contained in Table 1.

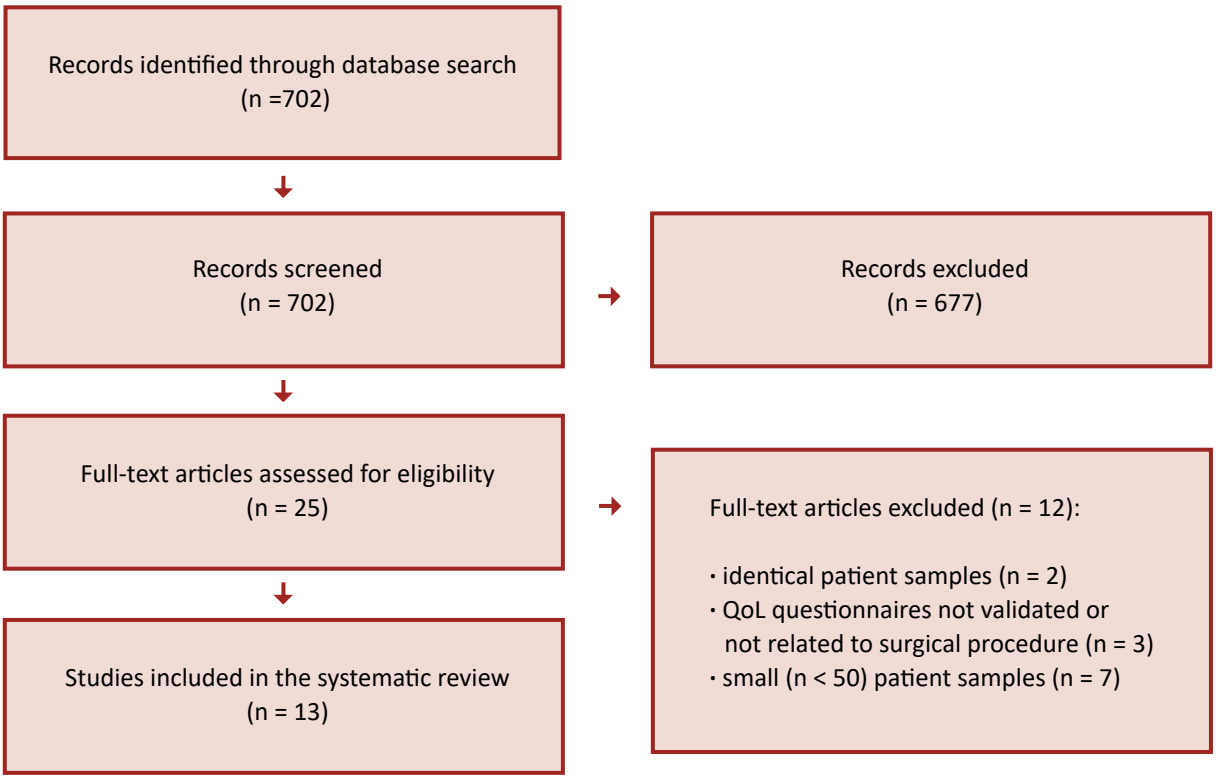

Figure 1. Literature search

Table 1. Data summary of included publications

Author	Year published	Patient number (F=Female M=Male)	Mean patient age (years)	Mean preoperative BMI [kg/m²]	Questionnaire type	Follow-up (months)	Preoperative (PRE) or Postoperative (POS) QoL analysis	QoL improvement (% of patients)
Akan S et al. [21]	2018	53 (F53)	34.85 ± 9.38	47.43 ± 6.37	SF-36	N/A	PRE + POS	Significantly improved ($p < 0.001$)
Bobowicz M et al. [30]	2011	84 (F63, M21)	39 ± 12.09	44.62 ± 8.17	BAROS	Mean 22 ± 6.75	POS	Improved (77.5% of "excellent," "very good" and "good" scores)
Charalampakis V et al.[22]	2018	95 (F50, M45)	37.4± 9.2	48.3± 7.1	Moorehead-Ardelt II	60	PRE + POS	Significantly improved ($p < 0.001$)
D'Hondt M et al. [27]	2011	83 (F61, M22)	40.4	39.3	BAROS, SF-36	Median 49 (17- 80)	POS	90.4% of "good" and "excellent" BAROS scores. The SF-36 scores for 'physical functioning' ($p = 0.030$) and 'general health perception' ($p = 0.017$) were better for the patients with a %EWL greater than 50%

Fezzi M et al. [23]	2011	77 (F54, M23)	42.4	47	SF-36, IWQOL-Lite	12	PRE + POS	Significantly improved SF-36 ($p < 0.001$) and IWQOL-Lite ($p < 0.001$)
Figura A et al. [19]	2016	59 (N/A)** 63 (F45, M18)	45.6 ± 10.9	51.5 ± 8.1	SF-8	Mean 19 ± 6	PRE + POS	Significant improvement in physical health ($p < 0.001$). Mental health did not change significantly ($p > 0.05$)
Fløl TN et al. [28]	2017	136 (F97, M39)	40.3 ±10.5	46.2 ± 6.4	SF-36	60	POS	Significant improvement ($p < 0.001$)
Gallart--Aragon T et al. [24]	2018	72 (F47, M25)	45.36 ± 9.38	N/A	GIQLI	6	PRE + POS	Significant improvement in total GIQLI score ($p < 0.001$)
Hosseini SV et al. [29]	2018	120 (F95, M25)	35.23 ± 10.05	48.87	Moorehead--Ardelt II, SF-36	Median 14.5 (2- 46)	POS	No significant difference in MAII score before and after operation (good to excellent in 90%). SF-36 scores were statistically different in all parameters ($p < 0.05$) except for 'role limitations attributed to emotional problems' and 'mental health' with no significant difference ($p = 0.080$, 0.074, respectively)
Kirkil C et al. [20]	2018	562 (F399, M163)	34.1 ± 8.1	45.4 ± 5.4	BAROS	Mean 7.4 ± 5.3	POS	Good to excellent BAROS score in 80.1% of patients. The mean QoL scores were significantly increased after LSG (range, $p < 0.05$ to < 0.001)
Porta A et al. *** [25]	2016	130 (F104, M26)	CL 39 ± 2.3 SI 36 ± 2.9	CL 41.01 ± 0.4 SI 40.09 ± 0.3	SF-36	12	PRE + POS	Significant improvement in all items of SF-36 in CL and SI groups (both $p < 0.05$)

Rebibo L et al. [26]	2016	56 (F44, M12)	43.3 ± 10.8	46.3 ±7.1	SF-36, BAROS	6	PRE* + POS	Significant improvement in all domains of the SF-36 questionnaire ($p < 0.01$). Mean BAROS score during follow-up = 7.1 (range: 4- 9)
Sofianos C et al. [31]	2016	103 (F88 M15)	41.8	42.1	BAROS	6	POS	Excellent to good score in 96.1%
Total		T = 1630 F = 1151** M = 416**						

***Preoperative data available only for SF-36**

****Gender results were corrected according to Figura et al. - N/A data of 4 excluded person gender**

*****Two groups of patients: CL= Conventional LSG, SI=Single incision LSG**

Quality of life

In The most frequently used questionnaires were SF-36 (in 7 studies), BAROS (5; twice authors used the updated version) and Moorehead-Ardelt II questionnaire (2). IWQOL-Lite, GIQLI and SF8 forms were used in one study each [11, 13-18].

Design varied significantly between studies with relatively short follow-up < 12 months in 6 studies and > 12 months in the remaining 7 studies. Majority of the articles (N = 8) included data for small study groups (50-100 patients), 4 studies had 100-200 participants and only 1 analyzed > 500 patients (Tab.1) [20]. Only 7 studies incorporated preoperative analysis of QoL [19, 21-26].

SF-36

The SF-36 questionnaire was used in 7 publications four times set together with another questionnaire [21, 23, 25-29]. Studies by Akan et al., Fezzi et al., Porta et al. and Rebibo et al. demonstrated significant improvement in all domains of the SF-36 in 6 and 12 months after surgery compared to preoperative scores [21, 23, 25-26]. Moreover, Akan et al. showed prominent postoperative improvement in the physical and mental components of the SF-36 questionnaire comparing with preoperative scores [21].

In a postoperative analysis by D'Hondt et al., patients with a percent excess weight loss (%EWL) > 50% at median 49 months of observation had higher SF-36 scores for 'physical functioning' and 'general health' perception [27]. Hosseini et al. compared a group of candidates for surgery with patients after LSG. SF-36 scores were statistically different in all parameters except mental health and role limitation due to emotional problems [29].

Fezzi et al. showed significant improvement in all domains of SF-36, but there was no statistically significant correlation between weight loss and the QoL [23]. Porta et al. additionally investigated the influence of classical or single incision LSG on QoL, showing no difference in QoL outcomes between the groups [25].

Fløl o et al. checked QoL 5 years after sleeve gastrectomy and compared it with a baseline cohort of obese patients eligible for LSG and a cohort representative of the Norwegian general population. The mental and physical summary scores were better at 5-year follow-up compared with baseline cohort but were below the normal results of the rest of the population. Authors showed no correlation between %EWL and HRQOL score at 5-year follow-up [28].

BAROS

The BAROS questionnaire was used in 5 studies, twice it was paired with the SF-36 [20, 26, 27, 30-31]. In 2 studies the authors used the updated version of BAROS [14, 20, 27]. In both versions this questionnaire merges %EWL, improvement of comorbidities, QoL in self-esteem, physical activity, social, labor and sexual

aspects, allowing complex assessment of outcomes in bariatric surgery.

The BAROS questionnaire was completed by patients in Sofianos et al. study with good to excellent outcomes achieved in 96.1% of patients at the 6-month follow-up and the mean BAROS score was 5.1 (range 1.9-8.7, max. possible score = 9) [31]. Rebibo et al. checked QoL after 6 months of follow-up using previous version of BAROS. Mean postoperative BAROS score was 7.1 (range 4-9) which means that the entire study group (56 patients) achieved an excellent outcome, although no precise information about the distribution of outcomes was included [26]. Slightly less optimistic results are published Kirkil et al. in their study on 562 respondents: "good" to "excellent" outcomes in 80% of patients (19.6% "excellent," 25.6% "very good," 34.9% "good") at 7.4±5.3 months of follow up [20]. Bobowicz et al. showed that "excellent," "very good" and "good" scores were achieved in 77.5% of patients, at the mean 22 months of follow up. In their study, females achieved significantly better result than males [30]. D'Hondt et al. also presented "good" to "excellent" score in 90,4% of responders at significantly longer time of observation with median of 49 months [27]. On the other hand, "fair" results were observed in 3.9-15.3% of patients in all studies, and failures varied between 0-13% [20, 30-31].

Moorehead-Ardelt quality of life questionnaire (MAII)

Moorehead-Ardelt quality of life questionnaire (MAII) was used in 2 studies [22, 29], once together with the SF-36 [29]. Charalampakis et al. showed significant improvement in QoL after LSG that was observed at all postoperative time points, despite the decline between the 2nd and the 5th year of follow-up. The MAII score increased from - 0.38 ± 1.3 preoperatively to 1.77 ± 0.8 (6 months), 2.08 ± 0.8 (12 months), 2.12 ± 0.7 (24 months) and 1.67 ± 1.1 at 60 months postoperatively. In final, there were only four patients classified with "poor" outcome and no patients in "very poor" group in MAII score at 5 years after operation. This study also showed that QoL improvement is higher in females [22]. Hosseini et al. showed that after median 14.5 months of follow up the median MAII score was 6.48 ± 0.45. Thus, the "good" to "excellent" scores were observed in 90% of patients but there was no statistically significant difference in comparison to control group [29].

Impact of Weight on Quality of Life – Lite (IWQOL)

Impact of Weight on Quality of Life – Lite (IWQOL) questionnaire in connection with SF-36 form was used by Fezzi et al. in their study with 12-month follow-up of 77 patients [23]. The scores of five areas of IWQOL-Lite showed an improvement of the quality of life connected to the loss of weight for all the dimensions: physical function, self-esteem, sexual life, public distress, and work. Their key finding is a significant change for every dimension of QoL, but there was no statistically significant correlation between the QoL and weight loss in 1-year follow-up. Researchers commented that the self-esteem was the only aspect of QoL that improved and was directly related to the %EWL [23].

The Gastrointestinal Quality of Life Index (GIQLI)

The Gastrointestinal Quality of Life Index (GIQLI) questionnaire was used by Gallart-Aragon et al. for evaluation of QoL before and 6 months after the operation. Authors showed significant improvements in all, except one aspect (emotional condition) of the GIQLI and total GIQLI score after half a year [24].

Short Form Health Survey (SF-8)

Short Form Health Survey (SF-8) was used by Figura et al. to assess and compare QoL in two groups of patients before and after LSG with outcomes of patients undergoing conservative treatment (i.e. dietary advice, physical exercise etc.). LSG patients' results, within-group comparisons, showed a significant increase in physical health, whereas mental health did not change significantly. For perceived physical health or mental health statistically significant post interventional group differences could not be identified. Important information is that four LSG patients failed to fill out the SF-8 questionnaire and were excluded from the analysis – there is no information about the sex of excluded patients [19].

Discussion

The LSG became a stand-alone procedure just in 2004. We aimed to find studies that have adequate follow-up time and did not include patients from the surgeons' "learning-curve" years. Therefore we focused on studies conducted in 2008-2018, when bariatric teams mastered the LSG technique.

QoL in bariatric surgery has been broadly investigated, nevertheless we couldn't find any review focusing directly on QoL changes following LSG [8-9, 32]. In the context of the epidemiological forecasts for obesity and the increasing implementation of LSG worldwide, it seems reasonable to intensify the research efforts on obesity treatment outcomes [5,

33-34]. The positive influence of bariatric surgery on obesity-related comorbidities is well known and QoL is an undisputable part of bariatric outcomes [35-37]. Evaluation of quality of life appears to be a very important parameter both for patients and surgeons. The same conclusion was made in review by Rausa et al, which compared quality of life after LSG and LRYGB [9]. The authors stated that there was no difference in QoL regardless which of the two surgical approaches was used. It leads to conclusion that patient's and surgeon's preference may play an important role in choice of surgical procedure [9].

Based on our literature review, we can state that almost all studies showed improvement in HRQOL after LSG in 6-80 months follow-up in adult population (Tab.1). It is easy to observe, mainly in studies using BAROS score, 77-96% of patients achieving "good" to "excellent" outcomes with improvement in the Moorehead–Ardelt QoL Questionnaire assessing such factors as self-esteem, physical activity, social engagement, ability to work, and sexual life. Sleeve gastrectomy shows promising results not only in pathological obesity but also class I obesity resulting in early weight loss and significant QoL improvement [38]. Some studies show that female patients achieve better QoL than male patients after bariatric surgery [22, 30]. LSG improves women's sexual function according to study by Akan et al., and reduces urinary dysfunction among males [21].

The benefit of LSG in terms of HRQOL improvement was also proven in older patients > 55 years of age, which interestingly was even higher than in younger groups [39-40]. Both studies also showed safety of this procedure in older patients. Similar outcomes such as resolution of co-morbidities and improvement in QoL were observed independently by Boza et al. in adolescents [41].

On the contrary, some studies demonstrated no significant difference in some aspects of QoL after LSG [19, 23, 25, 29]. What is even more interesting, Fløl o et al. showed that despite the significantly better HRQOL after LSG compared to the baseline cohort, the study population did not reach population norms [28]. In our opinion, this is a serious limitation of all HRQOL research in obese patients. Most of the researchers concentrate on the improvement of QoL after surgery with no reference to healthy volunteers neither to the pre-operative situation. This might be a goal for further research in obesity management.

Obesity surgery has some additional limitations influencing HRQOL such as worse food tolerance after LSG in up to 5% of patients in comparison to non-obese patients who had no surgery [27]. The very good news is that most recent studies show satisfactory postoperative reflux control in the majority of patients and low rates of de novo GERD after laparoscopic sleeve gastrectomy [37]. Currently there are several modern methods for data collection, follow-up and communication between surgeons and patients such as text messages or social media which could be considered in the holistic approach towards patients with obesity and present-day surgery [20, 42].

Major limitations of our study are: heterogeneity of all the reviewed studies, different designs and different QoL tools applied (six different HRQOL questionnaires) that bring in many sources of bias and make the results difficult to compare. Exclusion and inclusion of patients undergoing different bariatric procedures, lack of pre-operative assessment and non-uniform statistical reporting resulted in mainly descriptive and not quantitative analysis. Other limitations are small groups of patients included and different methodology used for quality of life data collection. Moreover, in some studies, there was limited or lacking information on patients' characteristics such as age, gender, BMI etc.

Conclusions

Despite all the limitations of the reviewed studies and different HRQOL tools used, almost all of the reviewed studies showed improvement in QoL following sleeve gastrectomy. It is difficult to assess which QoL tool is the most appropriate bariatric surgery patients. None of the tools assessed is perfect, but when used properly they can provide important information about postoperative course. Such information can then be used to adequately prepare for surgery and choose the best operative technique. Further research about this subject is needed, particularly controlled and long-term studies, with unified data collection and statistical analysis. In our opinion, quality of life after laparoscopic sleeve gastrectomy should be checked routinely during follow-up visits, same as BMI or %EWL.

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Conflict of interest

The authors declare no conflicts of interest regarding the publishing of this article.

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REVIEW ARTICLE

The relationship between blood pressure variability and outcome in acute ischemic stroke

Kamil Kowalczyk, Dariusz Gąsecki

Department of Adult Neurology, Medical University of Gdańsk, Poland

Abstract

Stroke is the second most common cause of mortality. Ischemic stroke is approximately 10 times more common than haemorrhagic stroke. The strongest risk factor for ischemic stroke is hypertension, thus reduction of blood pressure decreases the risk of ischemic stroke. However, the prognostic importance of blood pressure after is unclear. The problem is even more complex considering blood pressure variability (BPV), i.e. continuous changes of blood pressure values. The aim of this review is to discuss the very short-term, short-term, mid-term, and long-term blood pressure variability in the context of clinical outcome in patients after acute ischemic stroke. Most of the studies have shown that increased BPV in ischemic stroke patients is associated with poorer prognosis, however in some of them there was not association between BPV and outcome.

Keywords: outcome · ischemic stroke · blood pressure variability

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Introduction

Worldwide, stroke is the second most common cause of death, after ischemic heart disease, and the second most common cause of reduced disability-adjusted life-years [1-3]. In Poland in 2009-2013, an annual hospital admission rate of ischemic stroke patients (standardized by age) is 127/100,000 for females and 193/100,000 for males [4]. Hypertension is the strongest risk factor for ischemic stroke. In the INTERSTRO-

Corresponding author:
Kamil Kowalczyk, Department of Adult Neurology, Medical University of Gdańsk, Poland
e-mail: kkowalczyk@gumed.edu.pl

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KE study, self-reported history of hypertension occurred in 31.5% of patients with acute ischemic stroke (AIS), while the incidence of hypertension defined as self-reported history of hypertension or blood pressure (BP) > 160/90 mm Hg was even higher (45.2%) [5]. No Polish nation-wide data on the hypertension incidence in ischemic stroke patients are available, however in the years 2013-2014 the pre-hospital incidence of hypertension in Szczecin was 84.9% and 81.2% in Kraków {Formatting Citation}. Consequently, hypertension management reduces the incidence of stroke and therefore is recommended in primary prevention of ischemic stroke [8-10]. However, the prognostic significance of blood pressure in determining prognosis of stroke patients is unclear. The relationship between outcome and blood pressure often is U-shaped – both high and low early blood pressures may be associated with poorer outcome, yet the data results are inconsistent [11-13].

Furthermore, the management of altered BP in AIS remains challenging. Recommendations included in the current guidelines on BP treatment in AIS patients are not evidence-based [10, 15]. Present data suggest that lowering very high blood pressure in the early phase of AIS may be beneficial, but they need further confirmation. Data on raising blood pressure in the case of hypotension associated with focal cerebral ischemia are also inconsistent. Thus, due to insufficient data there is a continued concern about management of BP in patients with AIS [14]. Moreover, high blood pressure should be lowered for the purpose of secondary prevention after the acute phase of ischemic stroke or transient ischemic attack [10, 15].

Despite all the controversies, the role of BP and its management in acute stroke seems to be meaningful [13, 16-18]. However, not only casual BP measurements affect the prognosis after AIS, but also BP profiles may be an important factor. Evidence concerning their role in ischemic stroke is scarce.

There is a paucity of the available data on the course of BP in ischemic stroke. In the vast majority of patients, during the acute phase of ischemic stroke blood pressure usually rises during the first hours and then declines over the time (a phenomenon known as acute hypertensive response, occurring in over 60% of such patients) [19-20]. Blood pressure upon admission is higher in patients with a history of hypertension [21]. Moreover, decrease in BP during the first 4 hours after admission is seen in patients with mild stroke and with subsequent favourable outcome [21]. On the contrary, no decline in BP is observed in patients with severe stroke and unfavourable outcome [21].

The variation in blood pressure over time is known as blood pressure variability (BPV) [22]. The role of BPV in ischemic stroke is poorly understood. BPV was found to be higher in ischemic stroke patients receiving antihypertensives (without specifying the drug class) just before administration of thrombolytics [23]. More precisely, calcium-channel blockers decrease BPV and reduce the risk of stroke [24]. Longitudinal observations of the general population in Japan showed that increased BPV was associated with higher stroke mortality [25]. The aim of this review is to discuss the role of BPV in prognosis after ischemic stroke. Other interesting factors that may influence ischemic stroke outcome are changes of blood pressure during the sleep/wake cycle, however the topic is beyond the scope of this review and requires further study.

Indices of blood pressure variability

Blood pressure changes substantially between beats (very short-term BPV); minutes, hours or from day to night (within 24 hours, short-term BPV); between different days (mid-term BPV) or between clinic visits (long-term BPV) [26-27]. Indices used for assessment of BPV are as follows: standard deviation (SD), coefficient of variation (CV, defined as average SD divided by the mean BP and multiplied by 100), variation independent of mean (VIM, a transformation of SD which is not correlated with mean), average real variability (ARV, defined as the average of the absolute differences between successive BP measurements), successive variation (SV, defined as the square root of the average squared difference between consecutive BP measurements) [26, 28-30]. Novel approach includes more advanced methods, such as spectral analysis of the different frequency components [26, 31].

Patomechanism of blood pressure variability

There are several mechanisms having an impact on BPV; e.g., very short- and short-term BPV is caused by humoral, rheological, behavioural, and emotional factors; impact of reflex and central autonomic modulation or arterial elasticity; mid- and long-term BPV, by behavioural factors, arterial stiffness, as well as seasonal climatic change, or poor control of blood pressure in treated patients [26]. Detailed description of the BPV pathomechanism is beyond the scope of this review and may be found elsewhere [32-33].

Very short-term blood pressure variability

Dawson et al assessed beat-to-beat BPV in 92 acute stroke patients [34]. The subjects had Finapres non-invasive BP monitor fitted within 24 to 72 hours after symptom onset. SD of beat-to-beat recordings (SBP, DBP, pulse pressure and mean arterial pressure) was calculated. The patients were classified as dead/dependent or independent (mRS ≤ 2 points) on the basis of assessment at 30 days after stroke. Patients with higher DBP and mean arterial pressure variability were of greater risk of poor outcome.

Short-term blood pressure variability

In a Spanish study, Delgado-Mederos et al assessed the impact of BPV on enlargement of diffusion-weighted imaging (DWI) ischemic lesion and clinical outcome [35]. 80 stroke patients with occlusion of middle cerebral artery, treated with intravenous tissue plasminogen activator (tPA) were included into the study. All of them had DWI before and 36-48 hours after thrombolysis. Repeated SBP and DBP measurement were recorded for 24 hours since admission. BP variability was defined as SD of all BP measurements. In non-recanalized patients, SBP and DBP variability was higher than in recanalized patients. In the whole study population, higher SBP and DBP variability were associated with greater lesion growth on DWI. Interestingly, the correlation between BPV and DWI lesion expansion was higher in patients with persisting occlusion of the medial cerebral artery. In these cases, the correlation of SBP variability (but not of DBP variability) and lesion growth was still present after adjustment for baseline stroke severity, vascular risk factors, localisation of occlusion and the use of antihypertensives. Contrary to this, in patients who recanalized, DWI infarct size was not affected by BPV. Early clinical improvement (defined as a decrease of ≥ 4 points on the National Institutes of Health stroke scale [NIHSS] score at 24 hours after stroke onset) was correlated with lower BP variability. Moreover, higher SBP variability was associated with higher incidence of poor 3-month outcome defined as a modified Rankin scale (mRS) score ≥ 3. The associations of BPV and clinical outcome (early clinical improvement and frequency of 3-month poor outcome) were more evident in the non-recanalized study subjects.

Liu et al studied the impact of systolic BPV on severe haemorrhagic transformation after intravenous thrombolysis [36]. They included 461 patients and measured the following BPV parameters: SD, SV, average squared difference between rise and drop successive measurements (SVrise and SVdrop), and maximum of SV rise and SV drop (SVrisemax and SVdropmax) after quartering 0-to-24 h BP course. Severe haemorrhagic transformation (sHT) was defined as parenchymal haematoma or symptomatic intracerebral haemorrhage (haemorrhagic transformation and an increase of 4 or more points in NIHSS score). Unfavourable outcome was defined as 2-6 points in mRS at day 90. They found that SBP-SD and SBP-SV within 24 hours were positively associated with sHT. Within the first 6 hours, only SBP-SV, SBP-SVrise, and SBP-SVrisemax were associated with sHT. Higher SBP-SV, SBP-SVrise, SBP-SVdrop, SBP-SVrisemax, and SBP-SVdropmax among all studies periods (0-24h, 0-6 h, 6-12 h, 12-18 h, 18-24 h) were significantly associated with unfavourable outcomes at day 90 with the exception of SBP-SV drop 0-6 (no relationship).

Endo et al assessed the clinical outcome in stroke patients receiving intravenous thrombolysis (0.6 mg/kg dose of rt-PA, recombinant tissue plasminogen activator) and early BPV [23]. In the study, 527 patients were enrolled. BP was measured before administration of rt-PA and every 4 hours after completing the administration (in total, 8 measurements). Then SD, CV, and SV as the square root of the average difference in BP between each of the 8 successive measurements were calculated. Outcomes were as follows: intracerebral haemorrhage within the first 36 hours, modified Rankin Scale (mRS) score of 0 to 1, and death at 3 months. Higher systolic BPV (SD, CV, SV) was associated with symptomatic intracerebral haemorrhage and death.

In study by Manning et al, a post-hoc analysis of data from two randomized controlled trials (CHHIPS and COSSACS) was undertaken [37]. In COSSACS study, participants with stroke symptom onset < 48 hours were recruited, while in CHHIPS study, patients with symptom onset < 36 hours were enrolled. In both studies, baseline (prior to randomization) BP was measured (2 sets of 3 BP measurements, 10 minutes apart). The following BPV measures were obtained: SD, CV, ARV, and VIM for SBP and DBP. In both studies, the primary outcome was death or major disability (mRS > 3 at 2 weeks). Regarding COSSACS study, 706 patients were analysed. To assess the relationship between BPV and outcome, adjusted logistic regression was carried out. In the analysis, there was no statistically significant relationship between BPV and death and disability at 2 weeks. In terms of CHHIPS study, no association between short-term BPV and clinical outcome was found.

Tomii et al. evaluated impact of changes of BP on stroke outcome after intravenous (i.v.) thrombolysis [38]. 125 stroke patients who received intravenous rt-PA within 3 hours of symptoms onset were enrolled.

During the first 24 hours, BP parameters were measured (immediately after hospital admission as well as after starting rt-PA infusion: every 15 minutes during the first 2 hours, every 30 minutes from 2 to 6 hours, and every 1 hour from 6 to 24 hours). Then CV was obtained. The primary outcome was mRS < 3 points at 3 months, and the secondary outcome were as follows: early neurological improvement (a reduction of at least 4 points from the baseline NIHSS score or a total NIHSS score of 0 or 1 at 24 hours after i.v. tPA) and intracerebral haemorrhage (found on CT within 36 hours after i.v. rt-PA). In the analysis, CV of SBP and pulse pressure were positively correlated with intracerebral haemorrhage.

In another Japanese study, Tomii et al. investigated the effect 24-hour blood pressure on recovery from AIS. They enrolled 104 ischemic stroke patients admitted to hospital within 24 hours of symptom onset [39]. 24-hour ambulatory BP monitoring was started at 10:00 on the 2nd and 8th days of hospitalization. Subsequently, CV for SBP, DBP, and MBP was determined. The outcomes were independent activities of daily living (mRS ≤ 2 points) and poor outcome (mRS ≥ 5 points) at 3 months. In multivariate analysis, CV of pulse pressure on the second day was inversely associated with independent activities daily living.

Yong et al. investigated the relationship between BPV and functional outcome, mortality and haemorrhagic complications in 793 patients after acute ischemic stroke included in the ECASS-II study [40]. SV was used to represent BPV. 7-day haemorrhagic transformation and 90-day favourable outcome (mRS score of 0 or 1 point) as well as all-cause mortality were the end points. The results suggest that higher SBP-SV was related to the greater risk of parenchymal haemorrhage (PH) in rtPA-treated group and inversely associated with 90-day favourable outcome in the entire study population. On the other hand, in the placebo-treated participants, there was an inverse association between high SBP-SV and 90-day favourable outcome.

Kellert et al observed 427 patients with acute stroke and investigated the effect of BPV on the development of intracerebral haemorrhage (ICH) after intravenous thrombolysis [41]. BPV was defined as SV and maximum SV for SBP and DBP. Patients were divided into high (> median) and low (≤ median) systolic and diastolic BPV. ICH was diagnosed on the basis of neuroimaging studies, symptomatic ICH (sICH) was defined as detection of blood and NIHSS worsening by 4 or more points or leading to death. They found that there were no differences between non-ICH, ICH and sICH groups regarding BPV, however patients with high (> median) SBP-SD had increased risk of occurrence of sICH (p = 0.03). Moreover, lower SBP-SD was associated with independent functioning (mRS score ≤ 2) at day 90 (p < 0.001), and mortality at day 90 was more frequent in the high (> median) diastolic DBP-SD group (p = 0.04). The multivariate analysis for the 3-month outcome showed that high systolic BPV was associated with poor outcome.

In a more recent retrospective study of 215 patients de Havenon showed that increased SD, CV, and SV for SBP as well as increased SD and CV for DBP measured within 0-24 hours after admission due to AIS were associated with higher mRS assessed between 30 and 365 days [42]. Only patients with anterior circulation stroke were included in the study. The outcome was worse in the case of proximal artery occlusion and lower mean blood pressure.

In 2004, Castillo et al published their paper on the relationship between SBP, DBP, drop in BP and stroke outcome [43]. Their study included 304 patients with AIS admitted in < 24 hours after symptom onset. In all patients, BP on admission and on the first day was assessed. Reduction in SBP and DBP > 20 mm Hg between the first-day and admission measurements resulted in higher frequency of early neurological deterioration defined as a decrease in the Canadian Stroke Scale (CCS) score ≥ 1point within the first 48 hours after admission, increased infarct volume and worse outcome (CCS ≤ 7 points at 3 months).

In a retrospective study of 2545 ischemic stroke patients by Kang et al, the association of SBP-SD calculated on days 1, 2, and 3 and early neurological deterioration (END, increase of ≥ 2 points in NIHSS score) at days 1, 2, and 3 was checked [44]. It was shown that higher SBP-SD at day 2 was associated with END at day 2, and SBP-SD at day 3 was associated with END at day 3.

Buratti et al. evaluated 89 ischemic stroke patients with internal carotid artery occlusion [45]. They found that higher values of SD and CV for both SBP and DBP calculated within 48 hours after disease onset were significantly associated with poor outcome assessed at 3 months using the mRS score.

Sare et al. investigated the relationship between blood pressure variability and outcome in ischemic stroke patients admitted to hospital within 8 hours from symptoms onset who received placebo treatment instead of rt-PA [13]. Systolic and diastolic BPV was calculated as CV over 24 and 72 hours. At day 7, neurological impairment (NIHSS > 7); and at day 90, functional outcome (good, mRS ≤ 2; and poor, mRS > 2) were obtained. It was shown that (after adjustment for age, sex, time to inclusion, baseline NIHSS, hypertension in history, antihypertensive treatment within the first 7 days) increased systolic BPV was associated with poor 90-day functional outcome but not with early neurological impairment.

Mid-term blood pressure variability

Chung et al. evaluated the relationship between BPV and early neurological deterioration (END). In the study, patients with acute ischemic stroke hospitalized within 24 hours after symptoms onset were enrolled [46]. Finally, in the study period (over 3 years), 1161 patients were analysed. Blood pressure was measured for 72 hours of hospitalization. The following blood pressure variability parameters were calculated: standard deviation (SD) and coefficient of variation (CV) for SBP and DBP. END was defined as an increase of at least 2 points in the NIHSS score or increase of at least 1 point in the level of consciousness or motor items of the NIHSS, or the occurrence of new neurological deficits within the first 72 hours after admission to hospital. The study showed that all BPV parameters were higher in patients with END than in patients without END. Furthermore, SBP SD, SBP CV, DBP SD, and DBP CV were linearly associated with END, even after adjustment for mean BP and potential clinical variables (among others, age, sex, history of stroke or transient ischemic attack, diabetes mellitus, atrial fibrillation, Trail of Org 10172 in Acute Stroke Treatment [TOAST] classification, and baseline NIHSS score).

Ko et al assessed relationship between BPV and haemorrhagic transformation (HT) in ischemic stroke patients [47]. The authors enrolled 792 patients hospitalized within 24 hours after stroke onset whose initial gradient echo MRI showed no haemorrhagic transformation. BP was measured during the first 72 hours and the following BPV parameters were obtained: SD and average squared difference between successive measurements (SV) for SBP and DBP. Presence of HT and microbleeds was evaluated on all brain images carried out within first 2 weeks after stroke. The analysis showed that higher DBP SD and DBP-SV were associated with HT. The relationship remained significant for DBP-SD after adjustment for mean SBP, age, time from onset to admission to hospital, initial stroke severity, diabetes mellitus, stroke subtype, thrombolysis, initial glucose, and total cholesterol.

In the TAIST trial, the relationship between BPV defined as SD of SBP and early outcome (at day 10) was assessed [48-49]. In the study, 1479 patients with acute ischemic stroke were randomized. Death or neurologic deterioration (decrease of ≥ 5 points in the Scandinavian Stroke Scale [SSS] or decrease of > 2 points in consciousness part of the SSS) and neurologic deterioration alone were associated with increased SBP variability in univariate analysis and after adjustment for baseline prognostic factors, time to treatment and treatment assignment (high-dose tinzaparin, medium-dose tinzaparin, and aspirin). Recurrent stroke (ischemic, haemorrhagic, or unknown type) was associated with higher SD of SBP in univariate logistic regression, but the relationship lost its statistical significance after adjustment for the aforementioned factors.

In another study by Kang et al, the effect of BPV in the subacute phase of ischemic stroke on the 3-month functional outcome was assessed [50]. 2271 participants hospitalized within 48 hours of symptoms onset were enrolled into this retrospective observational study. The subacute stage was defined as the time period after 72 hours from ischemic stroke symptom onset to discharge or transfer to rehabilitation unit. SD and CV of systolic and diastolic blood pressure were obtained. Clinical outcome was assessed at 3 months using mRS. Poor outcome was defined as a 3-month mRS score of 2 to 6 if the baseline NIHSS score was ≤ 7 points, mRS score of 3 to 6 if the baseline NIHSS score was 8 to 14 points, and mRS score of 4 to 6 if the baseline NIHSS was ≥ 15 points. The analysis revealed that patients with poor outcome had a wider range of BP variability than those with good outcome.

A post-hoc analysis of data from ECASS-I study was performed by Yong et al [51]. The correlation between BPV and good functional recovery (mRS score of 0 or 1) at day 90 in ischemic stroke patients was assessed. BPV was defined as SV. Decreased diastolic SV between 0 and 72 hours predicted favourable outcome. Besides, similar relationship was observed for systolic SV, but only in patients treated with rt-PA.

Fukuda et al assessed the relationship between the in-hospital day-by-day blood pressure variability during the acute and subacute stage of ischemic stroke and poor functional outcome at 3 months [52]. They included 2566 patients with acute ischemic stroke and measured BP daily as well as its variability (defined as SD, CV, and VIM). Then the authors evaluated 3-month functional outcome based on mRS. They showed that higher BPV during the subacute stage (but not during the acute) was associated with worse long-term functional outcome after ischemic stroke, independently of age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, estimated glomerular filtration rate, ischemic stroke subtype (cardioembolic or non-cardioembolic), infarct area (anterior or posterior circulation), antihypertensive agents administered during days 1-3, the baseline NIHSS score, thrombolytic therapy, and mean BP. Higher SD, CV, and VIM of SBP were also associated with neurological deterioration (defined as an increase in the NIHSS ≥ 2 during hospitalization) after adjustment for confounding factors.

Tziomalos et al. assessed the relationship between BPV in the acute phase of ischemic stroke and the in-hospital outcome [53]. They evaluated SD and CV of

SBP and DBP in 608 patients during the first 2 days and the first 3 days after admission to the hospital. The outcome was in-hospital mortality and dependency rate (mRS score between 2 and 5). The authors found no association between BPV and the short-term outcome.

The relationship between BPV measured within 0-72 and 0-120 hours after admission and mRS was analyzed in the aforementioned study by de Havenon et al [42]. It was shown that higher SD, CV, and SV for SBP were predictors of poorer neurological outcome, while BPV for DBP was not significant.

In a prospective study by Wang et al, 873 patients with ischemic stroke were included in the analysis [54]. CV of SBP and CV of DBP calculated for the first 7 days of hospitalization were correlated with good neurological recovery (decrease in NIHSS score by ≥ 4 points from baseline or 0 point in NIHSS score), neurological deterioration (increase in NIHSS score by ≥ 1 point), poor functional outcome (2-5 points in mRS score) at 3 months as well as the risk of recurrent stroke, all-cause and cardiovascular mortality, and composite cardiovascular events (cardiovascular mortality, nonfatal stroke, and nonfatal myocardial infarction) within 12 months. They found that increased SBP-CV was significantly associated with less frequent good neurological recovery, neurological deterioration, poor functional outcome, higher risk of recurrent stroke and composite cardiovascular events. The same correlation was found for DBP-CV, except for association with poor functional outcome at 3 months (no correlation).

In another study, de Havenon et al. examined the relationship between SD, CV, and SV of SBP measured within 120 hours after admission in 110 patients with acute anterior circulation ischemic stroke with mRS score between 30 and 365 days [55]. Higher BPV was found to be associated with worse outcome, especially in patients with larger ischemic core volumes (defined as relative cerebral blood flow < 40% and absolute arterial tissue delay > 2 s) and larger hypoperfused volumes (defined as relative mean transit time > 135%).

Long-term blood pressure variability

In a 2014 study, the significance of long-term BPV in patients with ischemic stroke of all subtypes without atrial fibrillation was analyzed [56]. 632 ischemic stroke patients recruited within 14 days of presentation were included in the analysis. The patients were followed up (including BP measurement) every 3-4 months in an outpatient clinic (mean follow-up period was 76 ± 18 months). High BPV was defined as the fourth quartile of the study population. Outcome included all-cause and cardiovascular mortality, non-fatal recurrent stroke and nonfatal acute coronary syndrome. The analysis showed that higher SBP-CV was associated with higher incidence of all-cause and cardiovascular mortality. Furthermore, increased DBP-CV predicted the risk of cardiovascular mortality.

In another study, Lau et al assessed the relationship between visit-to-visit BPV and cardiovascular as well as all-cause mortality in patients with lacunar infarction [57]. 281 patients with lacunar infarction recruited within 14 days of presentation were followed up for 78 ± 18 months, on average. During each outpatient clinic visit made every 3-4 months, BP was measured and then systolic and diastolic BPV indices (defined as SD and CV) were calculated. Clinical outcome included all-cause and cardiovascular mortality, recurrent stroke and acute coronary syndrome. The relationship between BPV and clinical characteristics was assessed. Patients with a systolic (but not diastolic) BPV of the third tertile were associated with higher risk of all-cause and cardiovascular mortality. The relationship remained significant after adjustment for age, sex, mean systolic and diastolic BP, cardiovascular risk factors and cardiovascular-related comorbidities.

Meta-analyses

To our knowledge, only one meta-analysis for the influence of BPV in acute stroke on functional outcome exists was carried out to date [58]. Due to the heterogeneity of observational studies, the analysis included only 7 reports with one study on primary intracerebral haemorrhage [23, 34, 37-39, 50, 59]. It is noteworthy that only variability of BP within the first 7 days following acute stroke was assessed. It was suggested that higher BPV in patients with ischemic stroke is associated with worse functional outcome.

Summary

BPV was found to be a strong risk factor for stroke and other vascular events in high-risk patients, however little is known about the role of BPV after ischemic stroke [29]. Although some initial reports suggest their potential value in stroke prognosis, to date, few data on this issue are available and the existing results are inconsistent. Generally, the parameter which is most frequently reported as associated with prognosis after ischemic stroke is variability of SBP. In summary, it was shown that its higher values predict death, poor late outcome, haemorrhagic transformation, lesion growth assessed on MRI in case of occluded middle cerebral artery, neurologic deterioration or recurrent stroke [13, 23, 35-36, 38, 41-42, 44-48, 50-52, 54-55,

57]. Moreover, higher diastolic BPV was found to be associated with death, haemorrhage, poor short-term outcome and poor late outcome [23, 34-35, 42, 45-47, 50-52, 54]. Only several reports identified higher pulse pressure variability as being associated with haemorrhagic transformation and poor outcome. In one study, it was reported that higher values of mean blood pressure variability were associated with poor late outcome [34, 38-39]. On the other hand, many studies showed no prognostic value of at least some of BPV indices [13, 37, 41-42, 48, 52-54, 56-57].

In a significant majority of studies, variability indices of both systolic and diastolic BP were included [10, 20, 30, 32, 36-37, 40-43, 45-49, 51-52], but in four studies [36, 40, 44-55] only SBP variability was considered. One study group each evaluated the variability of SBP and PP; SBP, DBP, and PP; and SBP, DBP, and MBP [34, 38-39].

In most studies [10, 29-30,33-35, 39, 43, 46, 49, 52], only one BPV index of SBP and/or DBP was evaluated. In several studies, more than one BPV index was assessed (SD and CV in seven studies [36, 41, 45-46, 50, 53, 56]; SD, CV, and SV in three studies [23, 42, 55]; SD and SV in one study [47]; SD, CV, and VIM in one study [52]; and SD, CV, ARV, and VIM in one study [37]). In all of these studies, the importance of assessed indices was similar.

In general, majority of the studies regarding BPV are retrospective [10, 20, 31-32, 35-37, 39, 41-43, 45-46, 50], and the number of patients included in these studies is higher than in prospective studies [34-35, 38-39, 45, 52-54, 56-57].

As far as ischemic stroke subtype is concerned, in majority of the studies, this factor was not included in the analysis [10, 20, 31-32,34-37, 39, 43, 46, 48-49]. In several studies, BPV was found to be associated with the outcome after adjustment for, among others, stroke subtype [46-47, 50]. In one study, BPV was not associated with 3-month outcome independently of stroke subtype [38]. In few studies, only one stroke type was assessed: caused by middle cerebral artery occlusion [35] or internal carotid artery occlusion [45], lacunar [57], or anterior circulation ischemic stroke [55]. In one study, all types of stroke in patients without atrial fibrillation were included [56]. In one study, BPV was associated with long-term functional outcome independently of, inter alia, stroke subtype (cardioembolic vs. non-cardioembolic) or infarct area (anterior vs. posterior) [52]. In one study, it was shown that BPV did differ between stroke subtypes (anterior circulation, posterior circulation, or lacunar) and therefore they were not included in further analysis [34].

As demonstrated, studies of the relationship between BPV and outcome in ischemic stroke patients are very heterogeneous; however, the role of BPV seems to be important. Although no clinical trials assessing the effectiveness of BPV reduction in ischemic stroke were carried out to date, it is essential to identify subgroups of patients in whom its influence is highest and who might benefit from such therapies.

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REVIEW ARTICLE

Acute cholecystitis in patients with diabetes mellitus – systematic review

Monika Łącka, Piotr Spychalski, Małgorzata Dobrzycka, Olga Rostkowska, Jarosław Kobiela

Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdańsk, Poland

Abstract

Introduction: According to the WHO, an estimated 422 million people are suffering from diabetes worldwide. Among them, the incidence of cholelithiasis is higher than in the healthy population. The aim of this literature review was to summarize the available evidence about acute cholecystitis in patients with diabetes. **Materials and methods:** This study adhered to the PRISMA guidelines. The course of hospitalization of patients with and without diabetes who underwent cholecystectomy due to acute cholecystitis was compared.Following information was abstracted from original studies: general study information, patient characteristics, complications, and recommendations for patients with diabetes. **Results:** Initial search provided 1632 results. After full text assessment, 40 studies met the inclusions criteria. Operative and postoperative complication rates were significantly higher among the diabetic patients. Diabetes is a risk factor for conversion from laparoscopic to open cholecystectomy method. The authors' opinions on elective surgery before the onset of acute cholecystitis symptoms are divided. **Conclusions:** Diabetic patients are at greater risk of developing complications. An individualized screening and treatment approach, as well as proper preparation of the diabetic patient for an elective cholecystectomy could have a positive effect on the outcome. However, the low quality of the data from the systematic review does not allow for meta-analysis, which is why we cannot draw strong conclusions.

Keywords: diabetes and metabolism · general surgery

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Corresponding author:
Monika Łącka, Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdańsk, Poland
e-mail: lackamonia@gmail.com

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Introduction

According to the latest World Health Organization data, an estimated 422 million people suffer from diabetes worldwide. The incidence of diabetes is increasing rapidly and it is estimated that the number of people with diabetes will double by 2030. Approximately 104 million new cases of gallbladder and bile duct pathologies are reported annually. Among people suffering from diabetes, the incidence of cholelithiasis is higher than in the healthy population and diabetes increases the risk of developing acute cholecystitis [1-5]. In this group of patients, complications of acute cholecystitis such as gangrenous cholecystitis, bacteriobilia, perforation and emphysematous cholecystitis are more frequent [3-5]. Therefore, acute cholecystitis seems to be a serious problem in diabetic population [6]. However, not many studies were published in the last 30 years on this matter. Moreover, it was reported that cholecystectomy in people with diabetes is related to a significantly higher number of intraoperative complications and almost 3 times higher number of postoperative complications [7]. Once again, the literature about these specific issues is limited.

The aim of this study was to systematically review the available evidence regarding acute cholecystitis in patients suffering from diabetes.

Materials and methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRIMSA) guidelines. We performed a systematic search of the PubMed and Web of Science databases to identify studies on acute cholecystitis in patients with diabetes mellitus published before September 1st 2019. Following search query was used: "(cholecystitis OR cholecystectomy) AND (diabetes OR diabetic) Articles written in languages other than English were excluded. Abstracts, case reports, conference papers, letters, and editorials were excluded during the initial screening of titles and citations. Duplicated results were removed using Mendeley Software. Only full text papers describing the course of hospitalization in patients with diabetes who underwent cholecystectomy due to acute cholecystitis were included in the review (see Figure 1). In the next step we compared the course of hospitalization of patients with and without diabetes who underwent cholecystectomy due to acute cholecystitis.

All steps of the literature search were performed by two independent researchers. Decisions regarding final inclusion were resolved by a consensus.

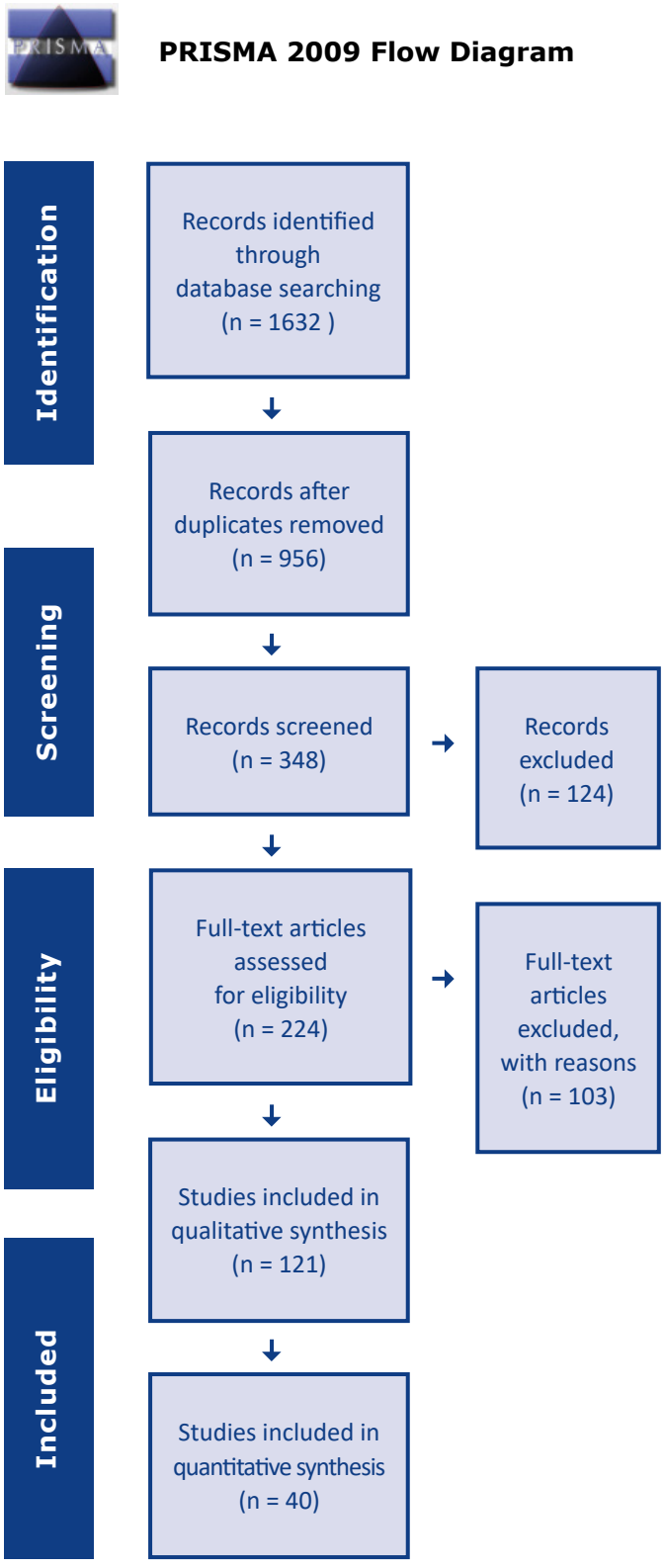

Figure 1. Flowchart illustrating the literature search

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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The following data was extracted from the original studies:

1. general study information: authors, publication year, country, institution,
2. demographics: number of patients, sex, age,
3. complications: septic shock, pneumonia, renal insufficiency, cardiovascular complications, (surgical site infection) SSI, wound dehiscence, infectious complications, conversion, preoperative perforation, bleeding, bile leakage, gangrenous cholecystitis, cholelithiasis, perioperative complications, postoperative complications, longer time of operation, anesthesia and total hospitalization time
4. recommendations for patients with diabetes: screening for gallstones, routine cholecystectomy before acute cholecystitis.

Results

The initial search identified 1632 articles. After excluding articles that do not match the criteria described above, 221 articles were included in the abstract review. Finally, 121 abstracts were selected for full text appraisal of which 40 met all the inclusion criteria and were included in this review. This systematic review included 40 articles including over 1300000 patients. 8 articles did not contain information on the number of patients enrolled in the study. In only 10 articles the patients were grouped by sex. The age of patients enrolled in the study was given in 9 of 40 articles. 22 papers out of 40 were published before 2010, 11 of which contain data from before 2000. In effect, 25% of the analyzed literature contains data collected more than 20 years ago (see Table 1).

Table 1. Reviewed articles key data

Authors	Number of patients	Men %	Risk factor of AC	Mortality	Infectious complications during hospitalization	SSI	Conversion LC to open surgery	Postoperative complications
Cho JY et al. 2009 [4]	1059	46.36	YES, AOR 95% CI 1.802 (1.153-2.816)					
Bodmer M et al. 2011 [24]	22574	24.3	AOR for developing gallstone disease followed by cholecystectomy of 0.88, 95% CI 78-1.00, p = 0.05) that diabetes mellitus is not an independent risk factor for cholecystectomy.					
De Santis A et al. 1999 [11]	336	39.29	YES 11,6% vs. 4,8% respectively OR, 2.55; 95% CI, 1,39-4,67					

Karamanos E et al. 2013 [5]	5460	55.4	YES, NR	YES (AOR) (95% CI): 1.79 (1.09, 2.94), adjusted p = 0.022]	5.6 vs. 1.6%; AOR [95% CI]: 1.85 [1.53, 2.23]	On insulin vs. non-diabetics: 4.2 vs 1.6%; AOR [95% CI]: 1.80 [1.39, 2.34]		
Miguel-Yanes JM et al. 2016 [12]	611 533		YES, p < 0.001	After open cholecystectomy [OR = 0.82 (0.78-0.87)], but a higher IHM after laparoscopic cholecystectomy [OR = 1.18 (1.03-1.35)].				
Turrill FL et al. 1961 [36]	481			YES, NR	YES, NR	YES, NR		
Liu C-M et al. 2015 [22]	108850		YES, MALE p < 0.001	53,1 + D1:D31				
Bedirli A et al. 2001 [27]	862			YES, NR			YES, p = 0,012	YES, 0,0061
Terho PM et al. 2016 [9]	373						YES, OR 2.0 (1.2-3.6) p = 0.014	
Cucchiaro G et al. 1989 [14]			YES, NR	YES, p = 0.002				
Lyass S et al. 2000 [15]	601	26.29	YES, NR	YES, NR			NO, NR	YES, p = 0.055
Jaafar G et al. 2017 [37]	94557				YES, complicated diabetes p < 0.001 OR 3.177 CI 2.153–4.689, uncomplicated diabetes p < 0.001 OR 2.943 CI 2.368–3.657	YES, complicated diabetes (OR 1.435, CI 1.205-1.708), uncomplicated diabetes (OR 1.391, CI 1.264-1.530)		

Lee S et al. 2011 [16]	611		YES, p = 0,002 OR (95% CI) 1,960 (1,262-3,044)					
Ransohoff DF et al. 1987 [17]	311	51.12	YES, NR	NO, p = 0,55				NO, NR
Pagliarulo M et al. 2004 [3]	1337	53.1	NO, BMI, AGE, FAMILY, NR					
de Siqueira Corradi MB et al. 2019 [18]	2520		YES, adjusted model 2.68 < 0.001	53,1 + D1:D31				
Warren DK et al. 2017 [40]						Independent risk factors for SSI after cholecystectomy. Adjusted HR (95% CI) 1.53 (1.19–1.98)		
Paajanen H et al. 2011 [19]	2548		YES, < 0.0001	YES, p < 0.01	YES, NR		YES, p < 0.0001	YES, NR
Doran H et al. 2018 [20]			YES, NR	YES, NR	YES, NR	YES, NR	YES, NR	
Ismat U et al. 2016 [42]	120					Presence of diabetes mellitus did not significantly affect the onset of surgical site infection in patients undergoing laparoscopic cholecystectomy; p = 0.07		
Ibrahim S et al. 2006 [34]	1000						NO, but diabetic patients who had conversion had a significantly higher Hba1c (8.9% +/- 0.6%; p < 0.038)	
Philip Rothman J et al. 2016 [35]	460995						None of the studies were eligible for meta-analysis.	

Lipman JM et al. 2012 [31]							YES, p = 0,002 OR (95% CI) 1,960 (1,262-3,044)	

Abbreviations: AC – acute cholecystitis, AOR – adjusted odds ratio, CI – confidence interval, Hba1c - glycosylated hemoglobin, HR – hazards ratio, IHM – in- hospital mortality, NR – not recorded, SSI – surgical site infection, LC – laparoscopic cholecystectomy, OR – odds ratio.

Complications

In 19 of the analyzed articles, diabetes was discussed as an independent risk factor for acute cholecystitis and in 14 of them diabetes was confirmed as an independent risk factor for developing this disease [1, 8-19]. Two studies analyzed this correlation in detail and in one it was significant only for women ($p < 0,001$), while in another it was significant only for men ($p < 0,001$) [20-21]. On the contrary, in 3 studies diabetes was not confirmed as an independent risk factor for acute cholecystitis [22-24].

A total of 15 articles analyzed diabetes as a risk factor for conversion from laparoscopic to open surgery. in 10 studies diabetes was found to increase this conversion rate [6, 10, 25-32]. On the contrary, in 5 studies did not show that diabetes significantly affected the risk of conversion [16, 33-36]. However, in one of these studies it was noted that diabetic patients with higher levels of glycated hemoglobin had a significantly higher risk of conversion [35].

The problem of the number of postoperative complications in patients with diabetes was analyzed in 6 papers [6, 15-16, 18, 22, 32]. Authors of 4 articles noted that complications significantly more frequently affect this group of patients [6, 15-16,32]. In all 6 papers pointed out systemic infectious complications after surgery [10, 13, 27, 32, 37-38] and 5 of them concluded that patients with diabetes are more at risk of systemic infectious complications [10, 27, 32, 37-38]. Septic shock as a separately listed postoperative complication appears in one study and its incidence is reported to be significantly higher for patients with diabetes [39].

Surgical site infection (SSI) in patients with diabetes has been discussed by the authors of 8 papers. In 6 articles it was reported that diabetes is a risk factor for SSI [13, 37-38, 40-42]. In one paper diabetes did not affect significantly the incidence of SSI [33]. In another paper, the authors summarized that diabetes did not increase significantly the incidence of SSI during laparoscopic cholecystectomy [43]. Authors of 4 articles analyzed the problem of postoperative wound dehiscence [10, 27, 37, 39]. Three of them reported that it significantly more frequently affected patients with diabetes [10, 27, 37]. According to one study, respiratory complications were significantly more frequent in the group of patients with diabetes [33]. Cardiovascular events significantly more often affected patients suffering from diabetes according to 4 articles [10, 13, 37, 43]. The authors of all 3 papers which distinguished renal failure as a postoperative complication reported that the above problem significantly more often affects patients with diabetes [10, 39, 43].

In 9 studies, increased postoperative mortality in diabetics was analyzed. The authors of 7 of them reported that it is significantly higher in patients with diabetes [10, 15-16, 32, 37, 39, 43]. In one paper it was noticed that the mortality was increased only in patients who underwent laparoscopic surgery [13]. The authors of one paper did not observe the correlation between diabetes and increased mortality [18].

Surgical complications

Just 2 papers examined the problem of intraoperative complications and only one of them confirmed the association between diabetes and the increased incidence of intraoperative complications [27, 32]. Two studies did not find the link between diabetes and increased intraoperative bleeding [26, 33]. On the other hand, one paper reported that diabetes increases the frequency of bleeding during surgery [27]. The authors of 3 papers reported that pre-operative gallbladder perforation occurs substantially more frequently to patients with diabetes [9, 27, 32]. In 3 studies no difference in the duration of surgery in patients with diabetes was noted, however in one of these studies it was demonstrated that the duration of anesthesia in patients with diabetes is significantly longer [26-27, 32].

The course of hospitalization

Five studies analyzed the effect of diabetes on prolonged hospitalization after cholecystectomy. Two of those confirm that patients with diabetes require longer hospitalization [10, 26]. Whereas in the remaining 3 studies, no such correlation was observed [6, 27, 33].

Recommendations

Elective surgery before the onset of symptoms of acute cholecystitis is recommended in 3 papers [15, 44, 45]. Whereas in 3 other articles such recommendation is not made [18, 22, 48]. Three authors discuss routine screening for cholelithiasis [15, 22, 45], and two of those recommend it [15, 45]. In one paper, the authors point out that patients with diabetes should be operated by laparoscopy because it improves postoperative outcomes [32].

Discussion

The analyzed studies were very heterogeneous in terms of data quality and data reporting. Surprisingly many articles did not contain basic patient demographics, detailed methodology (e.g. patient inclusion/exclusion criteria) or full results presented in quantitative data. For these reasons it was impossible to perform a meta-analysis in addition to the systematic review and therefore to draw strong conclusions.

Most authors of the analyzed articles confirm that diabetes is a risk factor for acute cholecystitis, although some authors disagree [22-24]. Based on the literature reviewed, it seems that diabetes is an independent risk factor for acute cholecystitis. Most of the available literature suggests that diabetes is a risk factor for conversion from laparoscopic cholecystectomy to the open approach. Conversion was significantly more common in diabetics with higher HbA1c levels. The effectiveness of the patient's diabetes treatment affects the severity of biliary disease and can increase the risk of conversion. Postoperative complications seem to affect patients with diabetes more often. According to most authors diabetes is a risk factor for systemic infection, such as pneumonia or UTI. Diabetic patients significantly more often suffer from SSI, wound dehiscence and septic shock. Diabetes is an independent risk factor for impaired wound healing, which is therefore in agreement with the general view.

The results of the analyzed articles also support the well-known fact that cardiovascular events and renal failure significantly more often affect patients with diabetes. It is noteworthy that the authors also noted a significantly increased postoperative mortality among diabetic patients. This may be directly related to the more frequent development of the above-mentioned complications. Another explanation for the above phenomenon is the more advanced age and more associated diseases discussed by the authors.

Regarding the recommendations for the management of patients with diabetes, the authors disagree whether elective cholecystectomy should be routinely performed in patients with diabetes. Although the EASL 2016 guidelines do not recommend routine cholecystectomy, the higher number of complications and mortality suggests that diabetic patients could benefit from such management [46]. Despite the large population of diabetic patients worldwide, at this time there is not enough high-quality evidence on this topic to formulate the necessary guidelines. An individualized approach, cholelithiasis screening and elective surgery could benefit not only patients but also the healthcare system.

Conclusion

Patients with diabetes have an increased risk of developing acute cholecystitis. Furthermore, diabetic patients with acute cholecystitis tend to have more complicated course of the disease. An individualized approach and screening in selected cases, as well as elective cholecystectomy after proper preparation of the patient could have a positive effect on the outcome. However, the low quality of the data from the systematic review does not allow for meta-analysis, which is why we cannot draw strong conclusions.

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SHORT COMMUNICATION

Carotid access in Transcatheter Aortic Valve Implantation – an alternative to the gold standard. A single-center experience

Aleksandra Stańska[1], Aleksandra Wierzbowska[1], Radosław Targoński[1], Wojciech Karolak[1], Agnieszka Mickiewicz[2], Miłosz Jaguszewski[2], Dariusz Jagielak[1]

[1]Department of Cardiac and Vascular Surgery, Medical University of Gdańsk, Poland
[2]1st Department of Cardiology, Medical University of Gdańsk, Poland

Abstract

Background: Transfemoral access is regarded as the TAVI gold standard for the transcatheter aortic valve implantation (TAVI) procedure. However, other options for vascular access have developed in the last few years. Access via the carotid artery is one such alternative. **Materials and methods:** The study included 9 elderly patients who underwent transcarotid TAVI procedure at the Cardiac and Vascular Surgery Department of the Medical University of Gdańsk. Procedures were performed by a local Heart Team in a hybrid operating room under general anesthesia. Data was collected before the implantation and at discharge. **Results:** The mean patients' age was 81 years of age (64-88) and the mean logistic EuroSCORE was 10.8 (7-16). Implantations were performed with 100% device success rate. Intra-operative valve-in-valve procedure was performed in one patient; there were no access-related and valve-related complications during the surgery. Post-procedural complications included minor bleeding, hematoma and pneumothorax. Echocardiographic parameters were significantly improving after the procedure. The mean hospital stay was 5 days (2-7 days). **Conclusions:** Transcatheter aortic valve implantation via the carotid artery appears to be safe and effective alternative to standard TAVI vascular access.

Keywords: transcatheter aortic valve implantation · aortic stenosis · carotid artery · elderly

Citation

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Corresponding author:
Aleksandra Stańska, Department of Cardiac and Vascular Surgery, Medical University of Gdańsk, Poland
e-mail: astanska@gumed.edu.pl
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Available online: www.ejtcm.gumed.edu.pl

Introduction

Due to an aging population, the number of patients with symptomatic aortic stenosis (AS) continues to grow. Since transcatheter aortic valve implantation's (TAVI) introduction, it has become a well-established procedure for the treatment of severe symptomatic aortic stenosis, especially in the elderly high-risk patients' population. Currently TAVI is globally recognized as an effective and safe alternative to open heart surgery [1-3].

Transcatheter aortic valve implantation via transfemoral access is regarded as the TAVI gold standard [4]. Approximately 70% of TAVI procedures are performed using this approach [5]. However, a large number of patients with severe peripheral atherosclerosis and calcified vessels, significant descending aortic disease or physiological abnormalities of the vasculature are considered for alternative approaches [6-7]. As the TAVI experience in the last few years has significantly increased, so have the options for vascular access [2]. In cases of difficult anatomy of the femoral-iliac-axis the analysis of risk-to-benefit ratio suggests looking for alternative pathways. Considering the reported high mortality rate of the transthoracic approaches [8], transcarotid access was recently suggested as one the alternative options.

The first case of transcatheter aortic valve implantation via left carotid artery was reported in 2010 and was described as a last resort, when other approaches were unavailable [9]. Furthermore, it should be performed only after a rigorous cerebral arterial evaluation. However, it has been recently reported that transcarotid approach has very similar outcomes as the transfemoral one in regard to mortality and morbidity [10-11]. Moreover, Overtchouk, et al. proved that the frequency of cerebrovascular events after transcarotid TAVI was similar to transfemoral approach [12-13]. Considering this, transcarotid access seems to be a very attractive and effective alternative to the transfemoral gold standard.

The aim of this article is to present short-term results of nine transcarotid transcatheter aortic valve implantation procedures performed at the Cardiac and Vascular Surgery Department of the Medical University of Gdańsk from December 2016 to December 2017.

Materials and methods

Patients and study design

The study included nine patients with severe, symptomatic aortic stenosis, who underwent transcarotid transcatheter aortic implantation procedure. All the patients were disqualified from transfemoral or other alternative TAVI approaches, due to the extensive calcification of the ascending aorta and aortic arch (porcelain aorta) or poor peripheral access.

Computed tomography angiography and Carotid Doppler was performed on every patient in order to assess the possibility of transcarotid pathway.

All data was collected during a hospital stay – before the procedure and at discharge.

Transcarotid TAVI procedure

All TAVI procedures were performed by a local Heart Team in a hybrid operating room equipped with a heart-lung machine on stand-by. Implantations were performed under general anesthesia. An approximately 5 cm vertical incision above the left clavicle was made in order to expose the carotid artery.

The position of the prosthesis was confirmed using a contrast medium. After the implantation, a further bolus of contrast medium was given to assess the position of the valve and to estimate the paravalvular leak (PVL) and coronary ostia. After estimating the shape of the valve and possible PVL, the decision whether to carry out post-dilatation was made.

Results

Patients' characteristics and parameters at baseline are presented in Table 1. The variables are presented as frequencies (percentages) and means. The mean procedure time was *M* = 59 minutes (45-120 minutes) and the mean carotid artery closure time was *M* = 9,5 minutes (4-20 minutes). One patient required pre-dilatation, whereas post-dilatation was performed in two

Table 1. Preoperative characteristics and parameters (n = 9)

Age (years)	81 (64-88)
Male Female	7 (77.8%) 2 (22.2%)
Logistic EuroSCORE (%)	10.8 (7-16)
EuroSCORE 2	4.4 (1.6-10.6)
STS score	6.4 (0.9-8.3)
Carotid artery lumen diameter	7.1 (6.5-7.6)

Pulmonary hypertension	1 (11.1%)
Diabetes mellitus	2 (22.2%)
Renal dysfunction	2 (22.2%)
Coronary artery disease	9 (100%)
Chronic obstructive pulmonary disease	3 (33.3%)
Previous coronary surgery	1 (11.1%)
Previous coronary angioplasty	8 (88.9%)
Previous stroke or transient ischemic attack	1 (11.1%)
Atrial fibrillation	5 (55.6%)
Peripheral arterial disease	5 (55.6%)
NYHA classification	
I II III IV	- 3 (33.3%) 6 (66.7%) -
Conduction disorders (LBBB, RBBB, AVB)	0 (0%)
Pre-existing permanent pacemaker	1 (11.1%)
Aortic valve insufficiency (≥ mild)	1 (11.1%)
Mitral valve insufficiency (≥ mild)	9 (100%)

AVB – atrio-ventricular block, LBBB – left bundle branch block, NYHA – New York Heart Association functional class, RBBB – right bundle branch block

cases. Intra-operative valve-in-valve procedure (Fig. 1) was performed in one patient due to too low implantation. There were no vascular access-site complications nor valve-related complications. Procedures were performed with 100% device success rate.

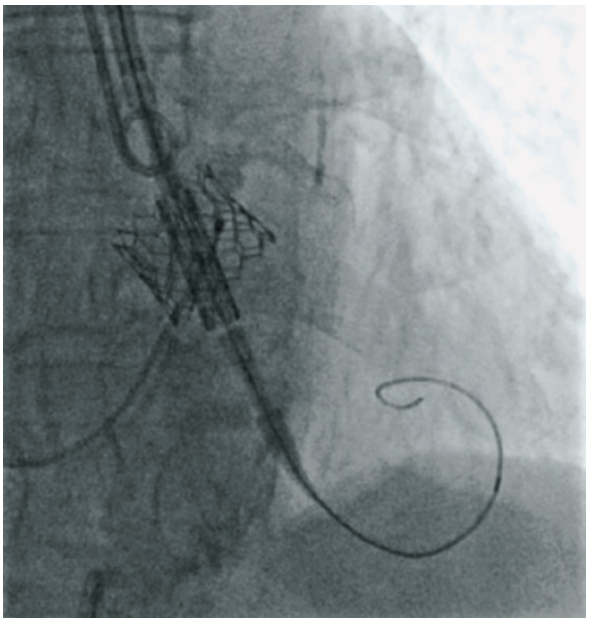

Figure 1. Intra-operative valve-in-valve procedure

Evolut R valve (Medtronic) was implanted in seven patients (78%) and SAPIEN 3 transcatheter heart valve (Edwards Lifesciences) was implanted in two patients (22%); six (67%) 29 mm sized valves were used, two (22%) 26 mm and one (11%) in 23 mm size.

Post-procedural complications included minor bleeding, hematoma which required surgical debridement and right-sided pneumothorax. Patients were discharged from the ward after approximately *M* = 4 days (2-7 days). The echocardiographic assessment at discharge confirmed good hemodynamic profile (Table 2).

Table 2. Echocardiographic aortic valve function before the procedure and at discharge

	Baseline (n = 9)	Discharge (n = 9)
Peak gradient (mmHg)	77.7 (67-95)	19.4 (13-22)
Mean gradient (mmHg)	46.8 (41-57)	11.1 (7-14)
Peak aortic velocity (m/s)	4.4 (4.1-4.8)	2.3 (2.2-2.4)
Effective orifice area (cm^2)	.78 (0.5-0.9)	1.8 (1.5-2)

Discussion

The main aim of the study conducted at the Cardiac and Vascular Surgery Department of the Medical University of Gdańsk was to evaluate the safety and hemodynamic parameters of the transcarotid TAVI procedure.

A high rate of procedural success and a small number of complications are presented. Furthermore, echocardiographic aortic valve function after the procedure was quite satisfactory. No patients experienced any neurological injury during, nor after the procedure.

It is well-known that the manipulation of carotid arteries may increase the risk of neurological injury, however the preliminary data suggest that patients undergoing TAVI procedure via transcarotid access are not exposed to severe neurological impairment. The key to success is probably thorough diagnostic process, including Carotid Doppler and computed tomography angiography. Assessing calcification and diameter of left carotid artery should be the most important part of the pre-operative qualification. In case of any doubts, it may be more adequate to choose non-vascular type of access.

The most important advantage of transcarotid access is a direct and a significantly shorter route to the aortic valve from the entry. The additional benefit is an improved movement precision during catheter delivery.

As in the case of every TAVI approach, there are also certain disadvantages of particular access. The transcarotid procedure is usually performed under general anesthesia and is more invasive in comparison to the transfemoral approach, which is conducted under local anesthesia. Assuming that TAVI should be a less-invasive procedure, the process of evaluation ought to be very specific and, in case of transcarotid access, exclude high-risk patients with a large number of comorbidities. Transcarotid pathway requires larger surgical intervention (Fig. 2) and hence wound-related complications may occur, thus may not be suitable for all patients disqualified from the traditional transfemoral access.

There are some limitations of the study. First of all, it is a single-center experience. Secondly, a small sample of patients was included. The analysis of a larger sample may offer slightly different results. Unfortunately, transcarotid access is still not considered as a common alternative to transfemoral approach, so the number of patients' undergoing TAVI via this access is quite small. Considering promising results this approach should be taken into consideration as a second- or third-choice access to the established gold standard.

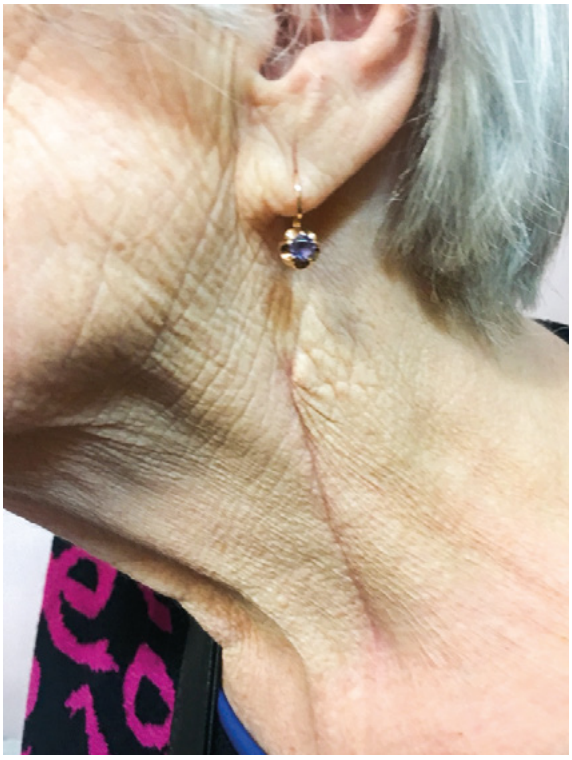

Figure 2. Transcarotid pathway requires larger surgical intervention

Conclusions

The preliminary data suggest that transcarotid transcatheter aortic valve implantation may be a safe and up-and-coming alternative to other types of vascular access. However, this requires further study and multi-center experience.

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COMMENTARY

Commentary on: The usefulness and limitations of diffusion tensor imaging – a review study

Tomasz Szmuda[1*], Shan Ali[2*]

[1]Neurosurgery Department, Medical University of Gdańsk, Poland
[2]Student Scientific Circle, Neurosurgery Department, Medical University of Gdańsk, Poland
*both authors contributed equally to the paper

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Abbreviations and acronyms

CPA – cerebello-pontine angle
DTI – diffusion tensor tractography
FN – Facial nerve

Dear Editor,

We read with great enthusiasm the review article by Sara Kierońska and Paweł Słoniewski about the limitations of diffusion tensor imaging (DTI) [1]. While it was brilliant, we felt that the paper could have benefitted from alluding to the role DTI of cranial nerves in cerebello-pontine angle (CPA) tumours.

If the facial nerve (FN) surrounds a tumour, it should be always preserved during a large CPA tumour surgery, although, sometimes it cannot be visualised intraoperatively. In such cases DTI might be particularly helpful. As researchers at the Medical University of Gdańsk, we were among the first to attempt FN tracking with DTI, however we obtained suboptimal results [2]. A 2018 systematic review on 234 cases, reported only a 90.6% accuracy of FN identification by fibre tracking DTI. For reference, the prediction rate of the FN's position in CPA tumours should reach 100% [3]. The current imaging capabilities of DTI are unsatisfactory and neurosurgeons should strive for better outcomes especially since concurrent radiosurgery enables similar CPA

Corresponding author:
Tomasz Szmuda MD, PhD, Neurosurgery Department, Medical University of Gdańsk, Mariana Smoluchowskiego 17, 80-214, Gdańsk, Poland
e-mail: tszmuda@gumed.edu.pl

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tumour control. At our department we tracked the FN in the operating room by integrating preoperative planning with a real-time neuronavigation system. This initially promising hypothesis, still unpublished, was ultimately disappointing as the prediction rate of about 80% was lower than expected.

Figure 1: The image illustrates the facial nerve's path tracked by diffusion tensor imaging as it courses around the vestibular schwannoma. Facial nerve predictions are presented on axial (A) and sagittal planes (B) (green bundles) and on a three-dimensional model (C) (segmented in orange volume). The debulking of the acoustic canal is presented in the intraoperative snapshot (D), the picture is injected to the screen is shown in the right upper corner.

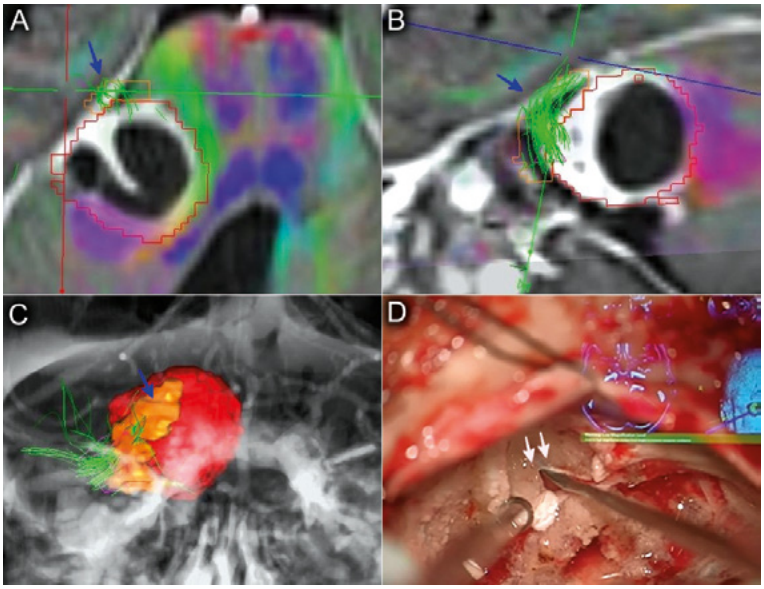

Figure 1. Facial nerve's path tracked by diffusion tensor imaging as it courses around the vestibular schwannoma. A – axial planes, B – sagittal planes (green bundles), C – a three-dimensional model (segmented in orange volume), D – the debulking of the acoustic canal

In cases where the accuracy of DTI is moderate, a combination of DTI with other imaging modalities might yield more reliable results. For instance, Pereira et al. complemented standard DTI with multiplanar fused sequences of magnetic resonance imaging; they took advantage of the regularity that only tumours enhanced with contrast could offer and thereby they isolated the surrounding cranial nerves [4]. This study of six patients postulates that the combined imaging with standard DTI could improve operative planning. While still a preliminary study, the agreement between the fused imaging and actual intraoperative anatomy proved to be correct always. We encourage scientists to experiment by combining the imaging potential of multiple modalities like DTI and magnetic resonance imaging. Perhaps together they can yield more accurate results than if used alone.

Regardless of our assessment, the study by Kierońska et al. contributes a relevant and critical appraisal of DTI. Radiological imaging like DTI is central to neurological surgery and we commend the authors for reviewing the limitations of it. We hope our commentary expands the scientific discourse on this topic, thus serving as another building block to advance the imaging standards of neurosurgery.

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