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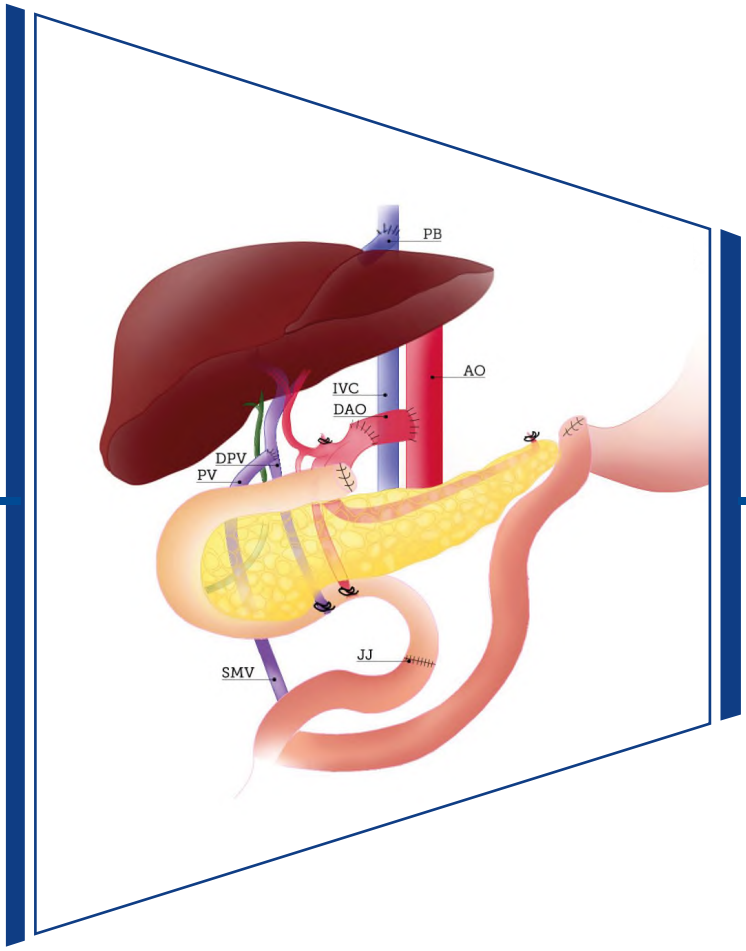

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CONTENTS

INVITED REVIEW ARTICLE

TECHNICAL REPORTS

RESEARCH ARTICLES

REVIEW ARTICLES

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2020;3(2):7-10

INVITED EDITORIAL

Thank God it's just COVID!

Alexander Donald Milliken

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Abstract

We have been lucky with the COVID-19 pandemic: it got the attention of the first world, yet (unlike other pandemics) has not threatened the very existence of humankind. COVID-19 has given us a chance to see how well we were prepared for something that was predictable.

Keywords: COVID-19 · Canada · pandemic · response · preparedness

Citation

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Graduating in medicine 55 years ago, I have lived through many epidemics. As a practicing psychiatrist watching what people say (or do not say) and using that information to make meaning, I know we have been lucky with the COVID pandemic [1-5]. It got the attention of the first world, yet (unlike others) has not threatened the very existence of humankind. It has given us a chance to see how well we were prepared for something that was predictable.

Epidemics occur regularly. In just the past 20 years, we have had SARS, MERS, swine flu, Ebola, H7N9 influenza, Zika, while dengue, malaria, measles, AIDS and TB continue and increase [2, 4, 6]. COVID morphed into a pandemic which affected us as well [4]. Some recent epidemics had a mortality rate of up to 40%; if they had spread like COVID, we would be facing the modern equivalent of the Black Death [7]. From most, Canadians have been protected by our geography, or poor viral human to human transmission, but with 6 such threats in the past 18 years, will luck protect us again from the next one due in 2025 or 2030 [8]?

Frankly, our response has shown many flaws that would be disastrous with a more malignant infection. To start, we avoided acknowledging it and being clear about the danger. If the Chinese government waffled, and it did, Canadian federal politicians also dithered to avoid bad news [9]. Other countries (and my province of BC) were calling for border closures and quarantining of travelers long before the feds acted. The Federal Minister of Health accused those asking about data reliability from China of pushing conspiracy theories, and later stopped Chief Public He-

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alth Officer Dr. Tam from answering questions about whether Ottawa had been warned that the national emergency stockpile, including PPE, had been underfunded - after we already knew that supplies were not rotated properly nor replaced [10]. Front line workers knew that supplies were scarce; the refusal to answer how long those supplies would last, and knowing they were unavailable in many care homes gave rise to legitimate fears which were not assuaged by political leaders of all stripes appearing like groundhogs sticking their heads out of their burrows, saying "We're here for you" and then disappearing again. This false reassurance was of little comfort for workers not only at an increased risk, but contributed to a continuing worry about workplace safety, which in some care homes led to the abandonment of their charges [11].

There was a gross lack of systemically collected important data. Some confusion is unavoidable with a new disease. But we know that the numbers of cases reported are unlikely to be the numbers infected, just those tested and found positive. Daily publication of deaths from around the world, while of great shock value, is even more suspect; we don't know how many extra deaths occurred without the infection being identified [12]. Deaths are clustered amongst those who are older, sicker, poorer and living in closer quarters, just as they are for any infection. In Canada, care homes for the elderly provide 80% of the fatalities; of the other 20%, greater numbers are amongst health care and personal service workers [11, 13]. We don't know why: working as they do, do they get increased viral exposure, and does this mean more serious illness? Is the lack of proper PPE a factor? Is it because of gender, or that many are from ethnic minorities? Is ethnicity a proxy for social disadvantage, or are there biological differences beyond melanin production [14]? Previous refusals to identify ethnicity in Canadian hospital data for purposes of virtue-signaling means we can only now start to ask [15].

Will there be a single second wave this fall or, like influenza, recurring waves? The long term trajectory of the illness – and our society – today is not in our hands: recurrences will depend on an as yet undiscovered successful vaccine, on how long immunity lasts and the level of immunity persisting in the herd [16]. With fewer compromised elderly left, previous epidemics have become less class or age conscious the second time around. Bending the curve has protected Canadian healthcare resources so we don't have the mass graves of Italy, New York or Brazil, scenes which would be familiar to a 14th century caller of "Bring out your dead". Yet our 14th Century response of closing the city gates, isolating the pest houses and avoiding those who might be affected (we call it lockdown and social distancing) has left us with deaths in solitary isolation, without family comfort or dignity [17].

If a second wave comes, as seems to be happening in Europe, the public health measures started three months ago will again flatten the curve, protecting health care services, but again at a great cost to society [18]. This playbook was written long ago, even before SARS. So, in 5 or 10 years' time, when COVID-19 hopefully becomes a memory, will we deal with the next plague better? We don't know what will cause it or exactly when, just that it will occur. If 10 years ago we knew what to do and had a negligent, ramshackle response, will we avoid it the next time?

As a 76 year old overweight physician, I do not want to die. Nevertheless, I prefer that COVID-19 affect me than my 46 year old child or my 16 year old grandchild. I have led my life, but if I die, I do not want to die alone, isolated, hungry, thirsty and in unchanged diapers. The deficiencies of the care home system have been well known for years; if the public report by the Canadian Armed Forces on the level of care came like a gut check, then the people in power were burying their heads in the sand [19]. For over 15 years, I have heard stories about colleagues visiting relatives in care homes daily to ensure care and that meals were eaten. Notwithstanding the calls from unions and politicians of the left, the care in the publically administered or non-profit institutions was only less inadequate than that in private ones. People of all political persuasions are advocating different solutions which reflect more their political world views than the reality of the data [20].

Here we come to the crux of this whole response problem: the first role of government must be to ensure that clinically appropriate standards, whether in public health, care homes or hospitals, are set in a transparent manner, and secondly to monitor and enforce those standards. This all governments, including many outside Canada, failed to do, including such simple standards as consistency of caregivers, time for care and adequacy of supplies [2, 21]. The dereliction of this important role by politicians of all stripes will not be solved by nationalization alone.

Not just business, but routine healthcare in Canada was been shut down due to a total lack of surge capacity. Every epidemic, including the annual flu outbreaks, produces a surge demand on the system [2]. For COVID, no-one can quarrel with the emptying of the beds to prepare for an unknown threat. What is obvious is that the system has been ground down so that this is the only way to deal with any surge, even seasonal flu. In 1970, Canada had 7 hospital beds per 1,000 population. By 1990, this had been reduced to 6, but by 2012, this number had been cut to an asto-

unding 2.7 [20]. This reduction occurred in spite of the fact that many patients today have more complex illnesses, or require more complex treatments which contribute to our greater lifespans. As a physician who practiced in 1970, I know that many conditions are dealt with more efficiently now: however, this enormous reduction in bed capacity has been not been driven by lower clinical demand but by the drive of politicians of all political parties to reduce taxes [22]. The court cases by the clinicians of the Cambie Clinic and the patients in the Chaouilli decision in Quebec arguing against the governmental health care monopoly were not about wanting to pay more, but to have reasonable access to care, and what to do if that access was not available [23]. While unions and politicians cast these cases as private versus public, at their core they are a discussion of what the standards should be, and how should they be upheld? Governments surreptitiously bury standards, dismiss clinicians' concerns and avoid collecting the data for the necessary public and transparent discussion about accountability.

Our response to COVID has been enormously expensive [24]. Small business owners have been pillaged, bankruptcies and financial distress have left proud people in tears. Routine healthcare was shut down and non-COVID deaths increased [25]. The future tax burdens to pay back the increased public debt are currently unknown. While an epidemic was predictable, preparation was ignored by those in political power, who should have been setting standards and enforcing them. The so-called "public administration" of healthcare enshrined in Canadian law has degenerated into political administration, without transparent accountability or a public source of truth. Five years ago, it may have cost a little more to keep adequate supplies of PPE, or provide good care in care homes. Today, we pay the price for not having done so.

Every unnecessary death is a waste. Every first responder or health care worker in unnecessary mortal fear is a cost. The COVID epidemic is bad enough, with an estimated infection fatality rate much lower than SARS or MERS [1-2]. For those who lost a loved one in isolated circumstances, each is a tragedy. But if we use it to demand three things: transparent accountability in the system; the provision of the essential requirements for a public healthcare system, and the elimination of the political legerdemain, next time we may be thankful COVID-19 came before COVID-25.

Acknowledgements

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TECHNICAL REPORT

En bloc liver and pancreas transplantation after total pancreatectomy with autologous islet transplantation

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Abstract

We present a patient with intractable and debilitating pain secondary to chronic pancreatitis who was effectively treated with total pancreatectomy with islet autotransplantation (TPIAT). Islets engrafted into his liver significantly contributed to improved blood glucose control and quality of life. Subsequently, the patient developed alcohol related acute liver failure and en bloc liver and pancreas transplantation was performed to replace the failing liver with engrafted islets. Pancreas transplantation was required to resolve his life-threatening severe hypoglycemic episodes. Herein, we detail an innovative and multidisciplinary management of this complex medical problem.

Keywords: Total Pancreatectomy with Autologous Islet Transplantation · TPIAT · liver and pancreas transplantation · chronic pancreatitis

Citation

Generette GS, Bachul PJ, Golab K, Basto L, Pyda JS, Borek P, Tibudan M, Anteby R, Perea L, Charlton M, Perez-Gutierrez A, Jayant K, Lucander A, Matthews JB, Millis JM, Fung J, Witkowski P. En bloc and pancreas transplantation after total pancreatectomy with autologous islet transplantation. Eur J Transl Clin Med. 2020;3(2):11-17.
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Introduction

Treatment of patients presenting with intractable pain due to chronic pancreatitis is complex and challenging [1]. Herein, we present an unusual clinical scenario, in which a patient who had a total pancreatectomy with islet autotransplantation (TPIAT) received a combined en bloc liver and pancreas transplantation due to liver failure. Once the pancreas graft failed, he required subsequent pancreas transplantation due to life threatening severe hypoglycemia. During the clinical course we employed innovative transplantation strategies, which have not yet been universally recognized by the medical community as the standard approach.

Case report

A 38-year-old, non-diabetic male with chronic pancreatitis and heterozygous CFTR (Cystic fibrosis transmembrane conductance regulator) gene mutation (p.R553c.1657C > T) was referred for intractable and debilitating pain persisting over five years despite multiple endoscopic interventions. The clinical course was complicated by malnutrition requiring enteral tube feeding. He had a BMI of 34 and a family history of non-alcoholic fatty liver disease (NAFLD). Computer tomography revealed an atrophic pancreas with calcifications and a non-dilated pancreatic duct. The patient underwent TPIAT: 152,000 islet equivalents suspended in 16 mL of tissue were infused into his portal vein (Figure 1A-D) [1]. The patient was completely weaned off opioid analgesics over the next few months and returned to full professional activity. Blood glucose was successfully managed with approximately 17 units of insulin per day and hemoglobin A1c (HbA1c) was 5.5% at 1 year follow up (Figure 2). Mild transaminase elevation was noted and attributed to NAFLD. His alcohol consumption during this period was approximately two drinks per day, three days per week.

Two years later, the patient was urgently hospitalized due to decompensated liver cirrhosis manifested by ascites, encephalopathy and hepatorenal syndrome. He had a MELD (Model For End-Stage Liver Disease) score of 42 (serum creatinine 2.7 mg/dL, total bilirubin 18.6 mg/dL, international normalized ratio 3.9). A liver biopsy demonstrated steatohepatitis with extensive fibrosis. The patient was thought to be ineligible for liver transplantation at a local center due to excessive alcohol use. Hospice care was initially advised; however, he was ultimately transferred to our center for re-evaluation.

We determined the patient to be an eligible candidate for liver transplantation consistent with recent progressive practice [2]. We reasoned that his acute liver failure was the initial presentation of liver disease and did not represent a failure of abstinence from alcohol- a traditional exclusion criterion for liver transplantation. Furthermore, in addition to alcohol consumption, his liver failure could have been multifactorial, reflecting the progression of nonalcoholic steatohepatitis, and be related to multiple metabolic derangements associated with his prior pancreatic disease. He underwent an emergent en bloc liver and

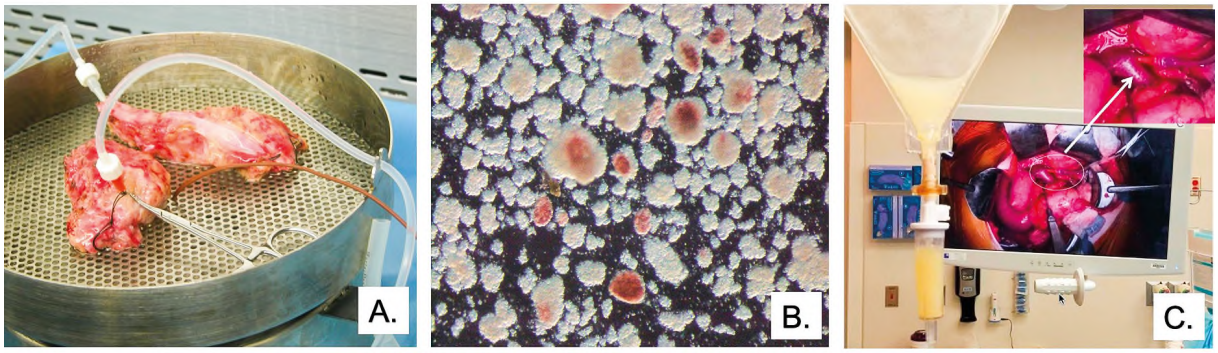
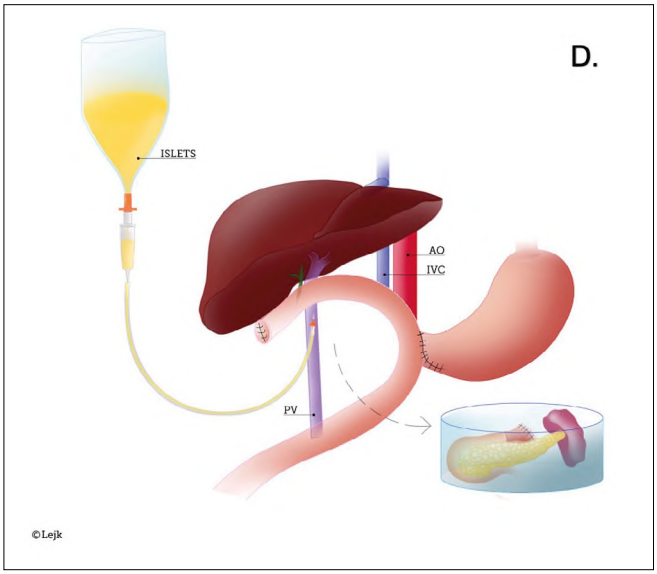


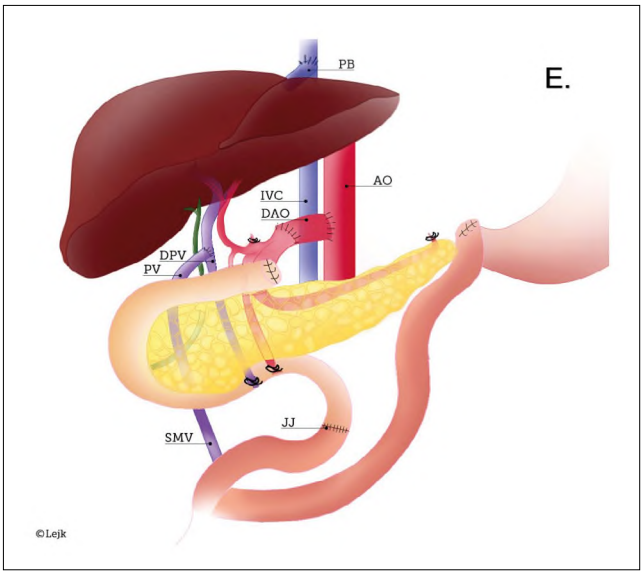
Figure 1 A, B, C. Major steps of islet isolation and islet transplantation

Panel A – Total Pancreatectomy. Excised pancreas after total pancreatectomy (TP) was transported to the Good Manufacture Practice (GMP) facility at University of Chicago for processing. The pancreas was divided, and the pancreatic duct cannulated and perfused with collagenase for enzymatic digestion and islet isolation.

Panel B – Islet Isolation. After digestion, a mixture of acinar tissue (light brown) and islets (stained with dithizone in red) was collected and the enzyme was washed off. The sample was tested for sterility and endotoxin and was suspended in transplant media in an infusion bag.

Panel C – Islet infusion. The portal vein (PV) was cannulated under direct vision and islets were infused intraportally. The white arrow points to the cannulated PV.





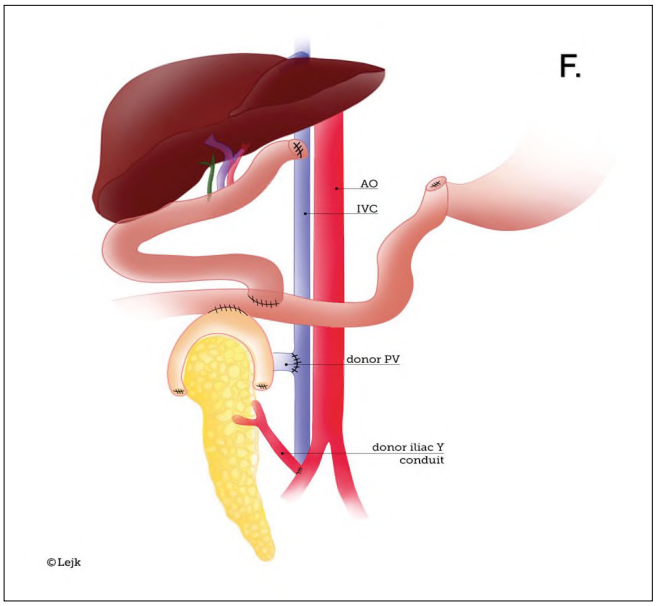


Figure 1 D, E, F. Illustration of TPIAT and en bloc combined liver pancreas transplantation and solitary pancreas transplantation procedures

Panel D – TPIAT. Schematic demonstrates pancreas excised with duodenum, distal stomach, and spleen and placed on the back-table. Next, pancreatic duct was cannulated for further processing in GMP facility. Once islets were isolated, they were placed in a bag and infused under gravity via the cannulated portal vein.

Panel E – En bloc liver and pancreas transplantation. After hepatectomy, the donor hepatic veins were connected to the vena cava using the piggyback technique (PB). The recipient's portal vein was connected to the side of the portal vein of the donor (PV/DPV). A donor aortic conduit (DAO) was used for the arterial supply to the liver/pancreas graft. Prior to the hepatectomy, the DOA was first anastomosed to the supraceliac recipient aorta (AO) and subsequently, the DOA was connected to a Carrel patch containing the donor celiac trunk and superior mesenteric artery (SMA) during liver/pancreas implantation. Roux-en-Y jejuno-jejunostomy (JJ) restored continuity of the gastrointestinal tract.

Panel F – Solitary pancreas transplantation. Schematic demonstrates the position of the transplanted deceased donor pancreas in the right lower abdomen. Arterial blood was provided to the graft via a Y-conduit made of donor iliac arteries. The portal vein of the graft is anastomosed to the distal cava and the duodenum to the side of the jejunum.

pancreas transplantation to compensate for both the impending loss of liver metabolic function as well as the sacrifice of the islet autotransplant during the explant of the native liver (Figure 1E). The cold ischemia time was six hours and we employed a porto-systemic veno-venous bypass for the transplant. The revascularization of the en bloc liver-pancreas graft was performed via the piggyback technique, with a porto-portal vein anastomosis and an aortic conduit to the recipient supraceliac aorta (Figure 1E). The small bowel was anastomosed to the side of the first loop of the donor jejunum. Due to significant hemorrhage from a friable aortic conduit anastomosis, pancreas graft warm ischemia was extended to 2 hours and the patient required extensive intra-operative vasopressor support and resuscitation with 23 liters of blood products. On post-operative day one, the patient developed hemodynamic instability and required re-exploration. The pancreas graft was found to be thrombosed and it was excised. The remainder of the post-operative course was uneventful, and the patient was discharged to a rehabilitation facility on post-operative day ten with steroid free immunosuppression.

Over the next several months, the liver graft function was excellent, but blood glucose control remained poor despite intensive diabetic care, including the use of MINIMED 760G insulin pump, 630G system

with SmartGuard® technology and Contour Next Link 2.4 glucose monitor. The HbA1c increased from 5.7% to 9.2%, and the patient experienced severe hypoglycemic episodes leading to seizures and an urgent hospitalization (Figure 2D). His quality of life was severely compromised with the progression of anxiety and depression, leading to a suicide attempt. Eventually, ten months following en bloc liver and pancreas transplantation, the patient underwent uneventful solitary pancreas transplantation in the right iliac fossa with enteric drainage (Figure 1F). Excellent glucose control was immediately restored and his quality of life improved. The patient has remained compliant with medical therapy for over three years now. Liver and pancreas graft function have remained stable with HbA1c maintained below 5% without exogenous insulin. Anxiety and depression were medically controlled and he remains abstinent from alcohol.

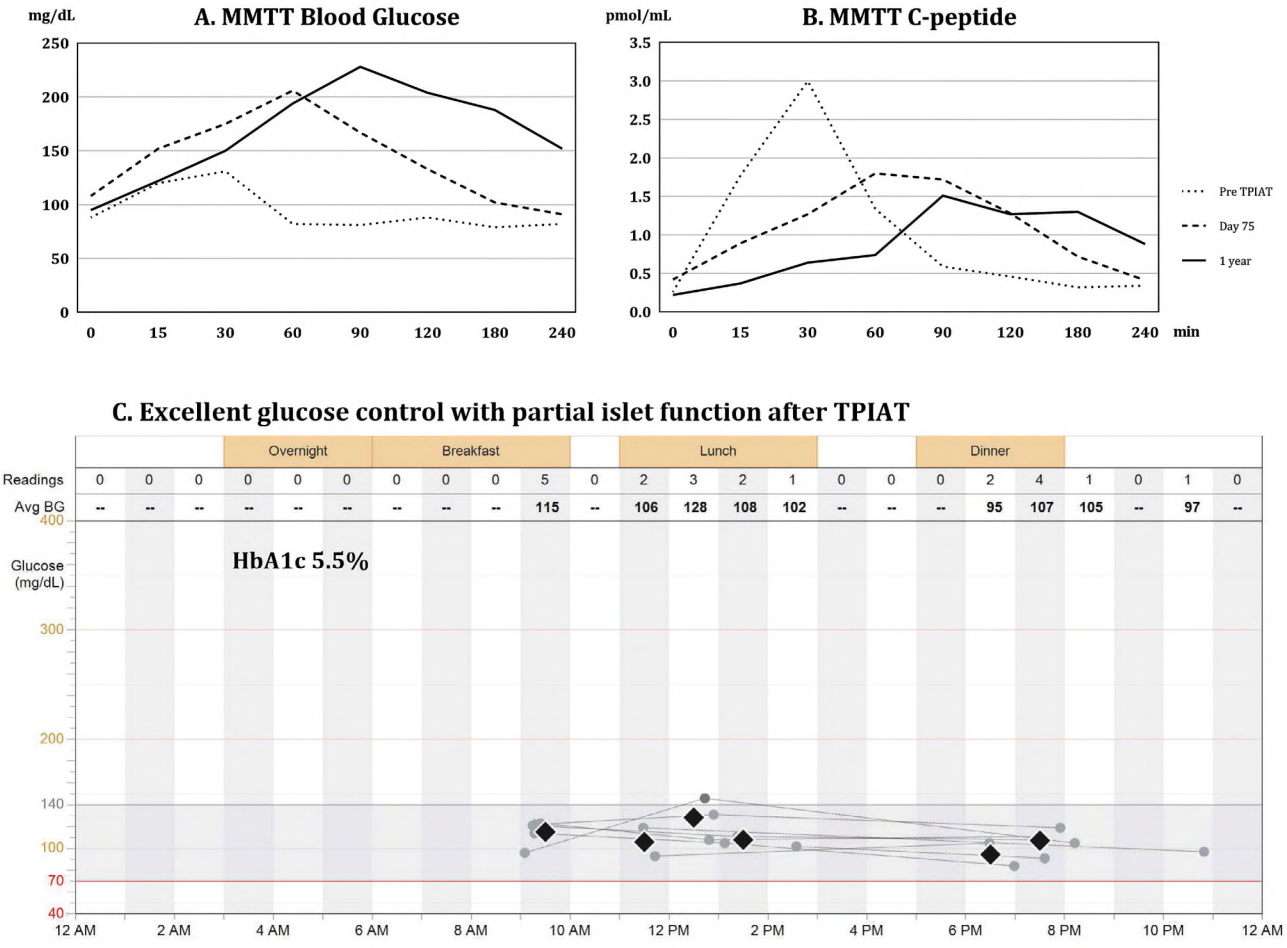


Figure 2 A, B, C. Metabolic testing of islet graft function and blood glucose control

Mixed meal tolerance test (MMTT) was performed prior to the procedure (dotted line), at postoperative day 75 (dashed line), and at 1 year (continuous line) after total pancreatectomy with islet autotransplantation (TPIAT).

Panel A presents blood glucose levels, whereas Panel B presents serum c-peptide levels during MMTT. Prior to surgery, islets controlled blood glucose during the mixed meal challenge; fasting blood glucose was 100 mg/dL, peaked at 120 mg/dL around 30 minutes after consumption of mixed meal, and dropped to normal values afterwards. This was demonstrated by levels of serum c-peptide, which corresponds to endogenous insulin released from islets (Panel A, B, dotted lines). After TPIAT, insulin released from the islet autograft, as represented by serum c-peptide (Panel B, dashed and continuous line), prevented a further rise of blood glucose above 230 mg/dL during the MMTT (Panel A, dashed and continuous line). The test confirmed partial islet graft function by demonstrating a clinically-significant insulin release from the islet graft and the need for exogenous support for optimal glucose control.

Panel C presents daily trends of blood glucose recorded over a period of one week in the patient after TPIAT with partial islet graft function, allowing for optimal glucose control (HbA1c 5.5%). Most of the time blood glucose remained within the normal range of 70-150 mg/dL, without episodes of hyper- or hypoglycemia.

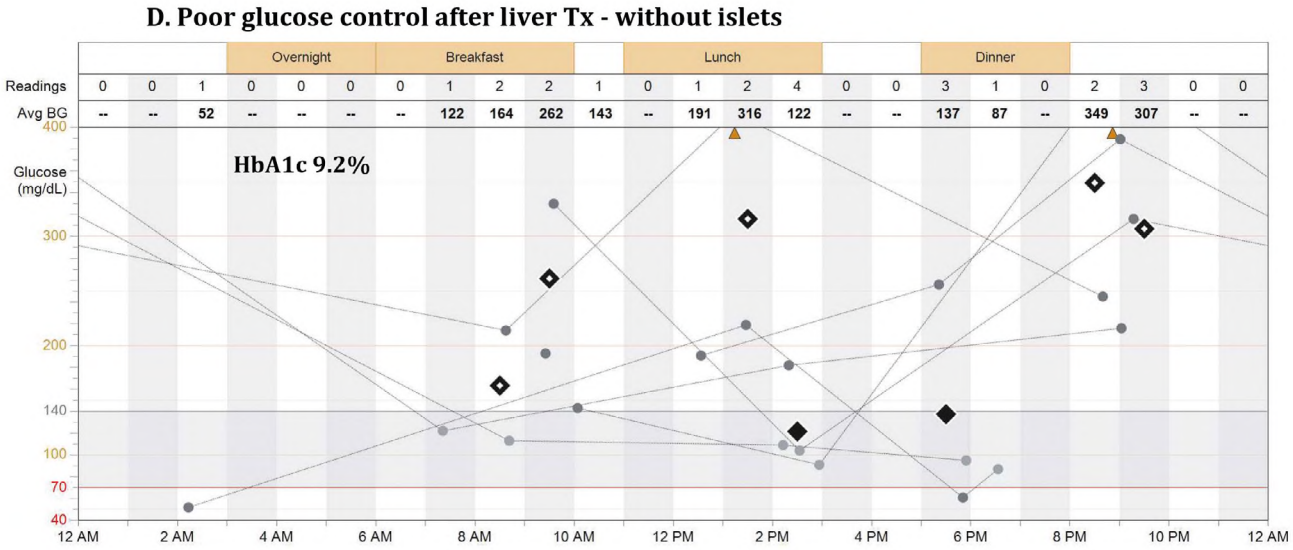


Figure 2 D. Metabolic testing of islet graft function and blood glucose control

Panel D presents extremely poor glucose control in the same patient following liver transplantation with hepatectomy of the liver, which contained the islet autograft. The patient struggled with insulin dose adjustments despite using an insulin pump, glucose monitoring system, and intensive diabetic care. He had persistent hyperglycemia (HbA1c 9.2%) with episodes of both severe hyperglycemia (> 400 mg/dL) and hypoglycemia (< 54 mg/dL) with loss of consciousness and seizures.

Discussion

Total pancreatectomy (TP) is an effective treatment for intractable pain due to chronic pancreatitis in properly selected patients [1, 3]. Progression of chronic pancreatitis is often inexorable, particularly when associated with underlying genetic mutations, and these patients are often the best candidates for this approach [4]. Indeed, our patient had benefited greatly from TP with complete resolution of pancreatic-type abdominal pain and opioid dependency permitting a return to full professional activity.

Since TP induces type 3c diabetes, simultaneous islet autotransplantation (IAT) is indicated to improve postoperative glycemic control. Despite IAT, most patients (60-80%) require insulin supplementation and hence some physicians and insurance carriers are hesitant to pursue IAT [3-5]. However, IAT reduces the amount of insulin supplementation required, and more importantly, restores a degree of counterregulation which protects from debilitating severe hypoglycemic episodes, as evidenced by our patient [3, 5-7]. This improves glucose control and helps to maintain normal HbA1c values [6]. The benefit of IAT extends beyond the 30% of patients who achieve insulin independence to an additional 50-58% who retain partial islet function (requiring some insulin support) [3, 5]. Overall, quality of life is notably improved in patients after TPIAT [3, 5, 7]. Contemporary evidence in the literature enormously values TPIAT and makes it essentially unethical to perform TP without IAT in otherwise suitable candidates. Furthermore, as immunosuppression is not required following the procedure, the additional risk of IAT is minimal and the rate of post-operative portal vein thrombosis is low and can be minimized with judicious post-operative anticoagulation [8]. Recognizing these advantages, the majority of commercial insurance carriers in the United States and in several European countries should consider reimbursing IAT. Hopefully, the multicenter TPIAT study, which is currently underway, will provide further evidence to change the position of the remaining insurance carriers (notably the Centers for Medicare and Medicaid Services) and clinicians who have not yet recognized the benefits of IAT [9].

Our patient benefited from partial islet function after IAT by achieving good glycemic control with the help of an insulin pump (HbA1c 5.5%) and improved pain control. However, the hepatectomy of the failing liver led to the loss of the islet autograft. Advanced diabetic care was needed but not able to provide sufficient glycemic control and the patient experienced extreme blood glucose liability and hypoglycemic seizures. Hence, our case provides invaluable evidence regarding the clinical benefit of even partial islet

function especially considering that the comparison is derived from the same patient who received the same advanced medical regimen.

Anticipating challenges in the management of diabetes after the excision of the failing liver with engrafted autologous islets, we performed pancreas and liver transplantation at the same time. Standard heterotopic pancreas transplantation in the pelvis is often challenging due to cardiovascular instability and congestion of the bowel during liver transplantation with extended overall operative time. Therefore, we decided to perform liver/pancreas implantation en bloc, which requires only the addition of an arterial conduit and one bowel anastomosis compared to liver transplantation alone [10]. Moreover, the liver confers a known immunoprotective effect for the same-donor organs transplanted simultaneously [11].

Even in completely stable patients undergoing solitary pancreas transplantation, the rate of pancreas thrombosis is 10% and results from increased vascular resistance coinciding with hemodynamic instability or reperfusion injury [6]. Timely excision of the necrotized pancreatic graft was critical for the intra-operative stabilization of our patient and his subsequent recovery. The re-operation only required an additional hepatico-jejunostomy, which was completed without interrupting any blood supply to the liver graft. Nevertheless, in future cases of patient instability, it would be judicious to perform the liver anastomosis first and defer the pancreas implantation until the hemodynamics improve. However, should the patient remain hemodynamically unstable or have a persistent vasopressor requirement, the pancreas graft can be implanted in a backup recipient.

Subsequent solitary pancreas transplantation proceeded uneventfully in our patient. Its benefits are well described for T1DM patients already on immunosuppression and in those with life-threatening episodes of severe hypoglycemia despite appropriate endocrine management [6, 12]. Our patient's clinical course highlights the continued advantage of pancreas and islet transplantation in diabetic patients who suffer from problematic hypoglycemia despite being on modern insulin delivery systems and glucose monitoring.

This case also supports the recent re-examination of a long-held paradigm of excluding active alcoholics from liver transplantation. Our patient was initially disqualified from liver transplantation at another center due to suspected alcohol abuse. Donor organ scarcity and high rates of recurrent liver failure in active alcoholics have led to a six-month sobriety requirement prior to consideration for transplantation. While this might be a reasonable approach for patients with chronic liver disease, it seems inappropriate if acute liver decompensation is the first manifestation of alcohol-related disease because such patients never had a chance to obtain proper treatment for alcoholism and meet the 6-month sobriety requirement. Recently published relapse rates are low and our patient's recovery supports the benefit of more nuanced criteria for liver transplantation in active alcoholics [13].

The etiology of the liver cirrhosis in our patient was multifactorial, including obesity, suspected NAFLD, and CFTR mutation carrier-status compromising pancreatic function which collectively contributed to liver failure [14]. Our patient suffered from steatorrhea despite enzyme supplementation, before and after TPIAT, which may have further contributed to steatohepatitis and its progression to cirrhosis as a consequence of choline deficiency, diminished phospholipid synthesis and failure of fat transport and oxidation [15]. Additionally, the patient had a history of alcohol consumption, which although moderate, may have exacerbated liver damage and led to progression of cirrhosis [16].

In summary, this case illustrates the numerous advantages of IAT and underscores its role in minimizing serious hypoglycemic events despite only partial islet graft function and persistence of post-operative insulin dependence. Furthermore, it demonstrates the value of liver transplantation in patients with acute liver failure secondary to alcohol. Lastly, it highlights the lifesaving role of pancreas transplantation in diabetic patients with problematic hypoglycemia and no remaining beta cell function.

Acknowledgment

We would like to thank Katarzyna Lejk for the graphic design of Figures 1D, 1E, and 1F.

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Disclosure

The authors declare no conflict of interest.

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TECHNICAL REPORT

First experience with left atrial arrhythmia ablation using a bi-directional steerable transseptal sheath (Vizigo) visible in the CARTO system as a method to reduce fluoroscopy

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Abstract

In this report we present ablations of complex left atrial arrhythmias in 3 male patients using the bi-directional steerable transseptal sheath (Visigo) which is visualizable by the 3D electro-anatomical system. Ablations of complex left atrial (LA) arrhythmias were performed in 3 patients. In the first 2 patients typical transseptal punctures were performed, followed by mapping with the LassoNav catheter and PVI (one patient also had isolation of the posterior segment). The last patient had a residual atrial septal leak, therefore ablation without fluoroscopy was attempted. An anatomical map of the right atrium was made. The ablation catheter and the Vizigo sheath were introduced into the LA through the leak in the septum. LA, pulmonary veins and 3 tachycardia loops were mapped. Lines were made in the roof of LA, in the mitral isthmus and within the atrial septum, restoring the sinus rhythm. Times of procedures/fluoroscopy were: 185, 185, 205min / 5.5; 3.8 and 0min. In the group of the last 10 previous ablations, these times were respectively: 209±48min/5,6±1,8 min. We conclude that the Vizigo sheath reduces the risk of electrode and sheath dislocation into the right atrium and the need for fluoroscopic verification during maneuvers performed with the sheath. It is also a step towards simpler left atrial ablation without the use of fluoroscopy.

Keywords: atrial fibrillation ablation · pulmonary vein isolation · zero fluoroscopy · steerable sheath · electro-anatomic mapping system

Citation

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Introduction

In this report we present ablations of complex left atrial arrhythmias in 3 male patients using the bi-directional steerable transseptal sheath (Vizigo by Johnson & Johnson, New Brunswick, USA) visualizable by the 3D electro-anatomical 3D system.

Material and methods

The first patient was a 70-year-old male with history of 2 pulmonary vein isolations (PVI) procedures, hypertension (HTN) and hyperthyroidism. The second patient was a 67-year-old male after PVI, with history of coronary artery disease and HTN. The third patient was a 71-year-old male with persistent left atrial flutter (LAFl) and history of PVI and HTN.

In the first 2 patients, short right atrium map was performed to create matrix for visualization of the Vizigo sheath (Figure 1A). Typical transseptal punctures were performed followed by mapping with the LassoNav catheter (Johnson & Johnson) and PVI (in the second patient also isolation of the posterior segment). Ablation Index algorithm was used and the distance between neighboring ablation points was < 6 mm. This strategy guarantees the continuity of the ablation line in the atria. The third patient had a residual atrial septal leak after previous procedure and was therefore attempted to ablate without fluoroscopy.

An anatomical map of the right atrium was made. On its basis, the Navistar ThermoCool SmartTouch SF ablation catheter (Johnson & Johnson) and Vizigo sheath were introduced into the left atrium through the leak in the septum (Figure 1B,C,D,E, Fig.2). The ablation catheter was replaced with a multipoint PenthaRay mapping catheter dedicated for high-density mapping (Johnson & Johnson) and an ablation electrode with a classic sheath was inserted through the same puncture (Fig.3). Left atrium with pulmonary veins and 3 tachycardia loops were mapped. Lines were made in the critical points of these loops: in the roof of the left atrium, in the mitral isthmus and within the atrial septum, restoring the sinus rhythm (final map – Figure 1D). Times of procedures and fluoroscopy were, respectively: 185, 185, 205 min / 5.5; 3.8 and 0min (dose area product, DAP: 76,4, 55,8 and 0mGy). To explain the meaning of these values describing the procedure, we present the values of these parameters in the last 10 patients who underwent similar procedures without the use of a Vizigo sheath. These times were respectively: 209 ± 48min /5,6 ± 1,8 min (DAP 52,9 ± 15,6 mGy). Procedural endpoints were achieved in all patients. There was no procedural complication noted.

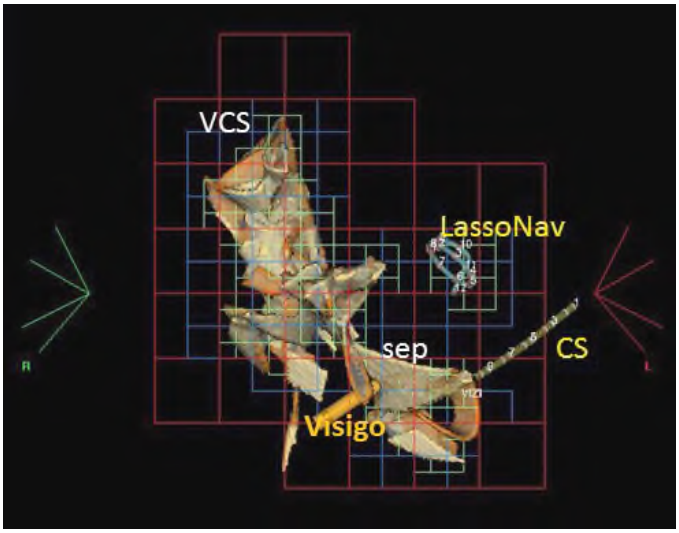

Fig.1A. AP projection. Matrix formed by Navistar SmartTouch ablation catheter and Lasso catheter (visible in the background as a colored grid) to accurately locate and visualize a steerable transseptal sheath. The fast-anatomical map of the upper part of the right atrium and the septum area is visible. CS – the coronary sinus dekapolar catheter, LassoNav – Lasso Nav catheter in the left atrium, sep – interatrial septum, VCS – the superior vena cava, Vizigo – bi-directional steerable transseptal sheath Vizigo.

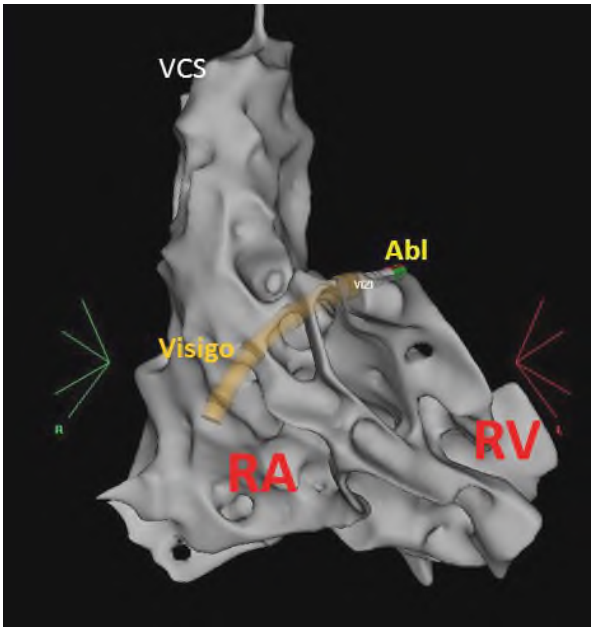

Fig. 1B. RAO projection of the fast-anatomical map of the right atrium. Vizigo sheath over the ablation catheter passing through the interatrial septum from the right to the left atrium. Abl – ablation catheter (Navistar SmartTouch) RA – the right atrium, RV – the right ventricle, VCS – the superior vena cava, Vizigo – bi-directional steerable transseptal sheath Vizigo

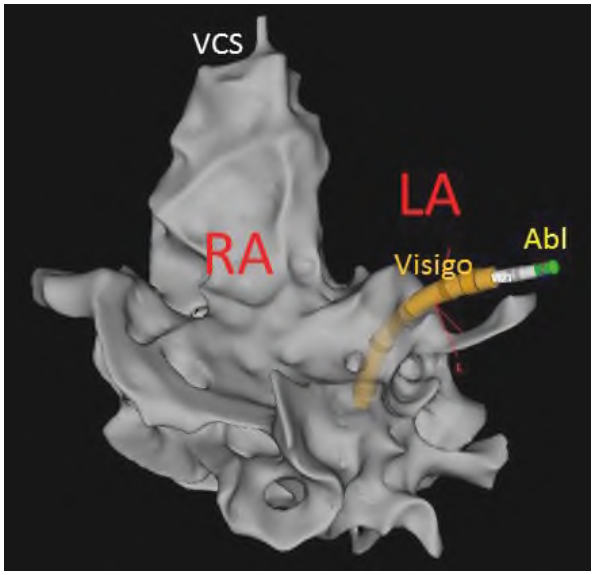

Fig. 1C. LAO projection of the fast-anatomical map of the right atrium. Vizigo sheath over the ablation catheter passing through the interatrial septum from the right to the left atrium. Abl – ablation catheter (Navistar SmartTouch) LA – the left atrium space (without the map at this level of procedure), RA – the right atrium, VCS – the superior vena cava, Vizigo – bi-directional steerable transseptal sheath Vizig

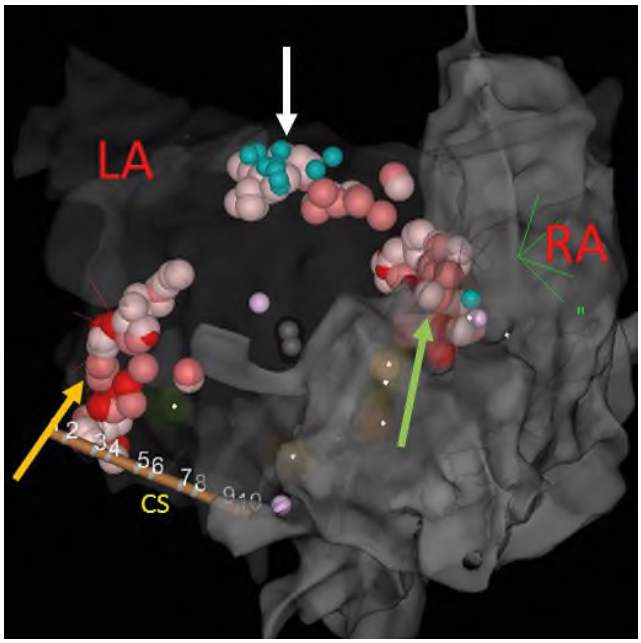

Fig. 1D. The final anatomical maps of the left (with transparency) and the right atrium after the procedure was finished. Modified posterior view. Small dots – places with fragmented potentials.
Larger blue dots – ablation points: white with ablation index 350-400, pink with ablation index 400-549, red with ablation index > 549. White arrow – the line in the left atrial roof. Yellow arrow – the mitral line. Green arrow - the septal line.
CS – the coronary sinus decapolar catheter, LA – the left atrium, RA – the right atrium

Discussion

Due to the harmful side effects of ionizing radiation we paid attention to the radiological exposure of the patients and medical staff during these procedures. This resulted in the introduction of the ALARA concept, which recommends rational minimization of fluoroscopy [1]. The aim is to perform the procedure with zero fluoroscopy [2]. Literature on fluoroless ablation of atrial fibrillation describes the use of intracardiac or transesophageal echocardiography in combination with an electroanatomical system [3-4]. However, the use of the intracardiac echocardiography significantly increases costs and adds complexity due to the use of an additional vascular puncture and an additional catheter. Transesophageal echocardiography is a significant discomfort for the patient and by triggering his/her cough reflex may increase the risk complications. Therefore, the introduction of a transseptal sheath visualized by an electroanatomical system may simplify such procedures and potentially increase their safety.

Conclusions

Based on our initial 3 procedures, we conclude that the Vizigo sheath reduces the risk of electrode and sheath dislocation into the right atrium and the need for fluoroscopic verification during maneuvers performed with the sheath. It is also a step towards simpler left atrial ablation without the use of fluoroscopy.

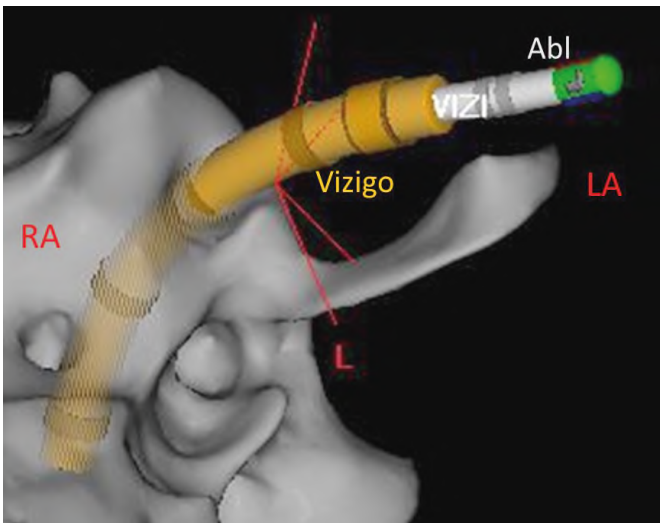

Fig. 1E. – enlarged region with Vizigo sheath (with ablation catheter inside) running through the interatrial septum.
Abl – ablation catheter (Navistar SmartTouch) LA – the left atrium space, RA – the right atrium, Vizigo – bi-directional steerable transseptal sheath Vizigo.

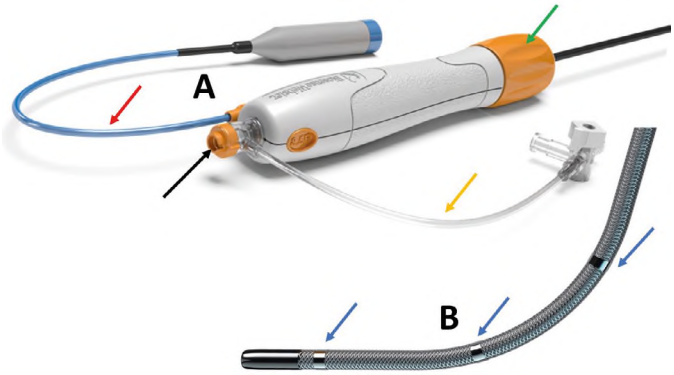

Fig. 2. Vizigo transseptal sheath.
A – Handle. Black arrow – lumen for catheter, red arrow – electrical cable connecting the sheath with the 3D system, yellow arrow – rinsing tube, green arrow – knob bending the sheath.
B – Distal steerable end with four distal electrodes (three of them are visible here) enable real-time steerable sheath visualization (blue arrows).

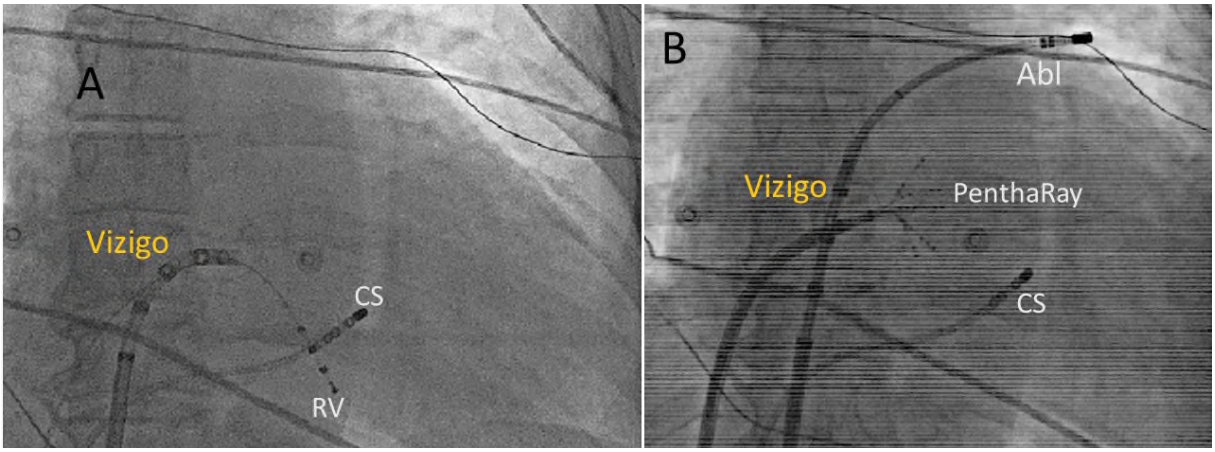

Fig. 3. Fluoroscopy picture presenting Vizigo sheath (example from another patient than presented in this report because our patient had ablation without fluoroscopy).
A – fluoro view with Vizigo catheter in the left atrium before introducing catheters there.
B – ablation Navistar catheter introduced via Vizigo sheath into the left superior pulmonary vein and PenthaRay catheter introduced via classical transseptal sheath.
Abl – ablation catheter (Navistar SmatTouh), LA – the left atrium space, RA – the right atrium, Vizigo – bi-directional steerable transseptal sheath Vizigo.

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RESEARCH ARTICLE

P wave duration and morphology in patients with atrial fibrillation

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Abstract

Background: Functional and structural atrial changes contribute to AF. It decreases conduction velocity and forms intra atrial blocks. In the ECG those changes are manifested by the duration and morphology of the P wave. **Material and methods:** The study group consisted of 50 patients with atrial fibrillation. There were 27 women and 23 men, aged 65.3 +/- 9.8 years. 22 patients had paroxysmal AF and 28 had persistent AF, in the latter direct current cardio version was performed. **Results:** In patients with a prolonged episodes of atrial fibrillation the P wave duration was longer in comparison to patients with sinus rhythm (187.1 +/- 31.5 vs 161.1 +/- 18.8 ms; $p = 0.006$). There were significant differences in P wave duration among the patients with normal and abnormal interatrial conduction, with the longest duration in complete Bachmann's bundle block group (152.7 +/- 17.5 vs 165.3 +/- 15.3 vs 207.9 +/- 27.5 ms; $p < 0.001$). **Conclusions:** In patients with persistent atrial fibrillation the duration of the P wave is prolonged in comparison to paroxysmal. In the majority of patients prolongation of the P wave duration is dependent on different forms of conduction block. The morphological changes of P waves are caused by the arrhythmia rather than left atrial hypertrophy.

Keywords: atrial fibrillation · P wave duration · P wave morphology · Bachmann's bundle

Citation

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Introduction

Functional and structural changes in an atrial muscle constitute a substrate for an atrial fibrillation (AF) [1]. These changes are the result of numerous diseases which mainly include hypertension, ischemic heart disease, further heart defects, and in particular a mitral valve disease, diabetes, myocarditis, heart failure or, less commonly, hyperthyroidism [2]. Despite the fact that we consider the atria as a whole, AF is mainly caused by pathologies that negatively influence the left atrium. The pathophysiology of a structural damage to the atrial musculature consists mainly in stretching its cavities, followed by necrosis and/or apoptosis of cardiomyocytes and replacing them by connective tissue cells [3-4]. This slows down the global conduction velocity of the activation wave, leading to slow conduction zones and focal conduction block, and contributing to the formation of re-entry circuits, which promote arrhythmias. The impact of the described phenomena on the isolation of junctional areas between the left atrium and pulmonary veins, ultimately with the formation of trigger zones in this area, proves to be very significant [5-6].

The structural changes described above contribute to the formation of arrhythmogenic foci, perpetuating premature beats, and to atrial rhythms. Rapid arrhythmias induce local changes in the refractory period of the atrial muscle, which, combined with the structural changes, increase the possibility of re-entrant rhythms and leads to the persistence of AF [7]. The arrhythmic paroxysms contribute to further enlargement of the left atrium by increasing left ventricle filling pressure, which then leads to consecutive structural changes.

As a result of the above-described processes, in the electrocardiogram (ECG) we can observe changes in the duration and amplitude of the P wave. Slow conduction and an enlargement of the left atrium are the causes of a prolonged P wave duration [8-9]. The pressure overload, especially in the hypertension, may induce atrial muscle hypertrophy which might be displayed as an increased P wave amplitude (an increase in the negative deflection in lead V1) [10]. However, a decrease in the number of cardiomyocytes and an increase in the content of connective tissue in the heart can lead to the opposite situation: a decrease in the P wave amplitude. Another issue is the appearance of intra- and interatrial conduction disturbances in the form of a partial or a complete Bachmann's bundle block. Changes in either the activation time or the direction of the conduction within the left atrium significantly affect the P wave morphology in the case of a complete block [11]. Assessment of the latter parameter has not been extensively reported in the literature so far. The purpose of our study is to assess the influence of the AF form on the duration and morphology of the P wave in the electrocardiogram.

Material and methods

We recruited into this study patients who were treated for AF at a single cardiology department in the years 2012-2020. The inclusion criteria were: paroxysmal or persistent (including long-term persistent) AF and the patients' consent. The exclusion criteria were: permanent form of arrhythmia, low symptomatic AF, lack of patients' consent. We took detailed history regarding the antiarrhythmic drugs the patient was currently taking, including propafenone and amiodarone. Patients' co-morbidities were noted. As the precise duration of an arrhythmia episode was not possible to establish, we included the patients with persistent AF lasting from 4 to 24 weeks.

The P wave duration and its morphology were analyzed using the LabSystem™ Pro EP Recording System (Boston Scientific, Marlborough, United States), where the ECG tracings allowed for assessing the sinus P waves. The P wave duration was measured in all leads at paper speed of 200 mm/s and enhancement of 64-128. The P wave morphology was assessed in lead II for the presence of notches (humps) and negative phases, indicating interatrial conduction disorders, known as Bachmann's bundle incomplete and complete conduction block. Another parameter was the amplitude of the P wave. Additionally, in Bachmann's bundle incomplete block the separation of the right and left atrium P waves peak was measured (if it exceeded 40 ms). In lead V1, the amplitude of positive and negative phases was also measured. To avoid any influence of accidental measurement inaccuracies, all the measurements were repeated 5 times and the mean value was calculated.

In patients with a persistent AF, direct current cardioversion was performed under general anaesthesia under propofol 1 mg/kg and fentanyl 50 µg administered intravenously. Single shock of 300 J was successful in all patients. The study was approved by the local Bioethical Committee at the Wrocław Medical University.

All continuous variables were presented as a mean and standard deviation. Comparisons were performed with the U Mann-Whitney test for independent groups or Kruskal-Wallis ANOVA for multiple comparisons. Any dependent comparisons were performed using the Wilcoxon paired test. All categorical variables were presented as numbers and percentages. The comparisons were performed with the chi-square test. P values < 0.05 were considered statistically significant.

Results

The study group consisted of 50 patients diagnosed with AF. There were 27 women and 23 men, aged 65,3+/-9,8 years. There were 22 patients with paroxysmal AF (in sinus rhythm during examination) and 28 patients with persistent AF, in whom the direct current cardioversion was performed in order to restore sinus rhythm. The clinical characteristics of studied patients were presented in Table 1.

In patients with a prolonged episode of the AF, the P wave duration was longer in comparison to patients with the sinus rhythm. The parameters and features of the P waves were presented in Table 2. The persistent AF group tended to have more pronounced interatrial conduction disorders but it did not reach statistical significance. In patients with the persistent AF, the positive amplitude in lead V1 was significantly higher than in patients with the paroxysmal AF. All other parameters did not vary between the studied patients. The direct comparison of positive and negative deflection in lead V1 in both groups according to AF form discriminated the borderline difference in group with the persistent AF (p = 0.061).

Table 1. Clinical characteristics of studied patients

	Patients with paroxysmal atrial fibrillation	Patients with persistent atrial fibrillation	P
Patients number	22	28	–
Sex	12-F 10-M	15-F 13-M	0.291
Age (years)	64.4+/-8.2	65.8+/-11.7	0.523
HT	19	24	0.458
IHD	4	9	0.312
HF	1	6	0.101
DM	5	6	0.824
CKD	3	3	0.692

Table 2. P wave parameters in the studied patients according to atrial fibrillation form

	Patients with paroxysmal atrial fibrillation	Patients with persistent atrial fibrillation	P
Number of patients	22	28	–
P wave duration (ms)	161.1+/-18.8	187.1+/-31.5	0.006
Number without Bachmann Bundle Block	6	4	0.799
Number incomplete Bachmann Bundle Block	11	14	0.532
Number complete Bachmann Bundle Block	5	10	0.322
Peak Separation (ms)	56.5+/-23.3	66.3+/-18.7	0.354
Amplitude II lead (mV)	0.150+/-0.161	0.109+/-0.037	0.464
Amplitude V1 lead positive (mV)	0.055+/-0.023	0.081+/-0.037	0.005
Amplitude V1 lead negative (mV)	0.049+/-0.021	0.061+/-0.036	0.304

The comparison of the presence of normal and abnormal Bachmann's bundle conduction did not yield any statistically significant result (16/22 vs. 24/28, p = 0.91). The parameters of the P waves presented according the interatrial conduction properties were presented in Table 3.

Significant differences in P wave duration were observed among the patients with a normal and an abnormal interatrial conduction, with the longest duration in the complete Bachmann's bundle block group. The differences in question inclined to be in concordance with an increasing age of the patients, even if the age of the patients, nor the other parameters (duration) were not statistically significant. While assessing the P wave morphology, an unexpected discovery was made. In 7 patients the features of the P wave did not meet the criteria of a double humped P wave as typically recognized in an incomplete Bachmann's block. We called them *triple-humped P* waves, as they exhibited three distinct peaks in lead II. An example of such morphology was presented in Figure 1.

Table 3. P wave parameters in all the studied patients according to interatrial conduction

	Patients without Bachmann's Bundle Block N=10	Patients with incomplete Bachmann's Bundle Block N=25	Patients with complete Bachmann's Bundle Block N=15	P
Age (years)	59.5+/-10.0	65.1+/-11.4	68.8+/-6.3	0.102
P wave duration (ms)	152.7+/-17.5	165.3+/-15.3	207.9+/-27.5	<0.001
Amplitude II lead (mV)	0.118+/-0.031	0.144+/-0.147	0.106+/-0.065	0.563
Amplitude V1 lead positive (mV)	0.070+/-0.039	0.070+/-0.037	0.069+/-0.027	0.993
Amplitude V1 lead negative (mV)	0.054+/-0.027	0.062+/-0.035	0.046+/-0.023	0.265

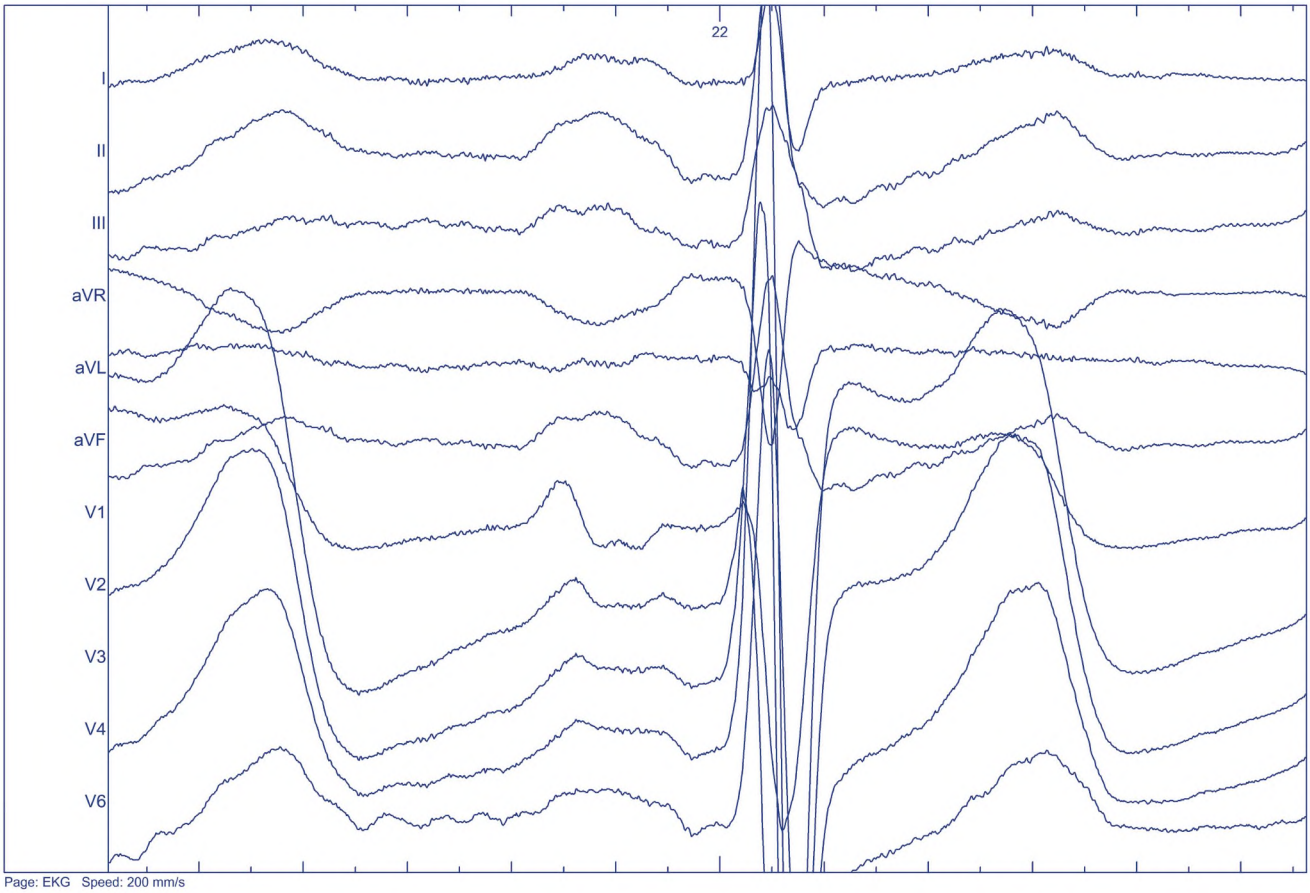

Figure 1. Triple humped P wave. Note the 3 peaks in P wave in lead II (present also in other leads). Paper speed 200 mm/s, magnification 64x.

The comparison of the assessed parameters of the triple-humped P wave in the studied groups were shown in Table 4.

The mean duration of the triple-humped P waves from the persistent AF group emerged to be longer than the single-humped P wave from the paroxysmal AF, but the number of patients did not allow the statistical analysis.

Discussion

Our key finding is the effect of an ongoing arrhythmia on the extension of the P wave duration of the electrocardiogram, indicating AF-induced intra-atrial and inter-atrial conduction disorders and, most probably, atrial enlargement. The latter phenomenon is clearly associated with an increase in the left ventricular filling pressure and is probably dependent on the ventricular rate [12]. Data on the effect of AF on the muscle conduction is more scarce and equivocal, though.

Due to the fact that the subgroups of patients with paroxysmal and persistent AF were comparable in terms of age, gender distribution, comorbidities, and antiarrhythmic treatment, which might have affected the duration of the P wave, it should be assumed that our observations are dependent only on the presence or absence of an ongoing arrhythmia [1]. This is in line with the clinical observation made years ago, contained in the in the term “AF begets AF” created by Wijffels et al. [13]. The electrical cardioversion itself had no effect on the duration of the P wave in one study as the parameter was stable immediately after the procedure and 24 hours later [14].

It should be borne in mind that the precise methodology for measuring the duration of the P wave adopted in our study is qualitatively different from the one that was used by other researchers [15-16]. It is not without reason that a few years ago we showed in a similar assessment the lack of P wave dispersion, which is related to the inaccuracy of the measurement [17]. In fact, this approach exactly corresponds to Bayes de Luna's suggestions in the paper “Diagnosis of interatrial Block” only from 2017 where it was explicitly ordered to measure the P wave from its earliest beginning in any lead to the latest end in any lead [18].

Another conclusion from our research is the fact that there is a significant relationship between the duration of the P wave and the separation of the right and left atrium peaks in lead II. Although the difference in the duration of this separation in both groups of patients turned out to be statistically insignificant and probably resulted from the percentage of patients with an incomplete conduction block in the Bachmann’s bundle in both groups, it seems to be obvious that the extension of the P wave peaks is mainly due to the prolongation of conduction in the bundle and not within the atrial muscle [19].

A further learning from our work is the increase in the amplitude of the initial phase of the P wave in lead V1. This seems to reflect the known electrocardiographic relationship. Under normal conditions, the overlap of the left atrial negative phase with the right atrial positive phase causes a decrease in the former. Only a significant increase in the mass of the left atrium increasing the negative deflection in V1 results in the formation of a typical configuration – with a negative predominance in this lead [8]. Interestingly, our results point at another important relationship. In both examined groups, the positive deflection in lead V1 is greater than the negative deflection in this lead. It speaks strongly for the possibility that among the patients examined by us, it is interatrial conduction disturbances and not hypertrophy, e.g. hypertensive hypertrophy of

Table 4. Triple humped P wave characteristics

	Patients with paroxysmal atrial fibrillation	Patients with persistent atrial fibrillation
Triple humped P wave (N)	1	6
P wave duration (ms)	158.3	176.6+/-13.2
Peak Separation (ms)	76	80.8+/-8.9
Amplitude II lead (mV)	0.088	0.106+/-0.026
Amplitude V1 lead positive (mV)	0.081	0.084+/-0.069
Amplitude V1 lead negative (mV)	0.056	0.060+/-0.042

the left atrium as a cause of AF [4-5], that are prevailing.

When analyzing the entire group of patients, it should be assumed that the presence and the type of conduction disorders in the Bachmann's bundle are responsible for the increase of the duration of the P wave. While there are no similar articles yet, and the only one referred to similar conclusions [20], this is consistent with the literature on Bachman's bundle conduction disorders [10-11, 19].

The analysis of the mean age in our group of patients without, with an incomplete, or with a full block of conduction in the Bachmann's bundle, even if not statistically significant, may indicate phases of dependence of the disease progression with age. The clear statistical relation could be expected with the increase of the number of patients. A more numerous group could make it possible to distinguish comparisons of patients with paroxysmal and persistent forms of the AF in subgroups derived according to the interatrial conduction status.

The presence of the triple-humped P waves have not been reported in the literature so far, even if the term 'thriphasic' (three-phased) was used in one animal experimental study by Pasławska et al. In the figure reported by them, the precise assessment shows a rather multiphasic pattern, as the initial phase is negative and the other two ones are positive [21]. In our small patients' series, the P wave morphology in lead II exhibits three more or less distinct positive peaks, indicating the activation of the left atrium through the Bachmann's bundle, with a kind of an additional conduction obstacle (compartmentation) in the left atrium. As we did not assess the anatomical and echocardiographic morphology of the atria, the final conclusion on the nature of the reported phenomenon remains uncertain and requires further research. Whether this observation has any clinical importance remains unclear and requires further study.

An important limitation of our study is a relatively small number of patients. As our assessment is based on a very precise measurement method using the electrophysiological recording system, we are aware that our results could not be directly comparable to the other authors' measurements. As we already mentioned, the duration of the persistent AF was not possible to be exactly established. Because we hypothesise that the extension of the P wave duration is mainly caused by the arrhythmia itself, it should be understood as the main limitation of our research, even if the available data contradicts such a correlation [14]. The other important issue, that was not mentioned in the study, was the influence of a prolonged PR interval on the risk of AF development. The combination of atrial and atrioventricular abnormalities should constitute the objective of a further investigation.

Conclusions

In patients with the AF, the duration of the P wave is prolonged. The persistent arrhythmia affects this parameter to a greater extent. In the majority of patients, the prolongation of the P wave duration is caused by different forms of the interatrial conduction block. The morphological changes of the P waves indicate the causal relationship of the arrhythmia rather with interatrial conduction disorders than with a left atrial hypertrophy.

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RESEARCH ARTICLE

Relation of cigarette smoking and mood disorders to cognitive impairment progression

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Abstract

Background: Both depressive disorders and nicotine use are proven and important risk factors of dementia. The purpose of this study was to verify if cigarette smoking and depression symptoms together are disadvantageous for the prognosis in mild cognitive impairment. **Material and methods:** A total of 43 patients with a diagnosis of mild cognitive impairment were included in the study. ADAS-Cog was performed upon inclusion in the study and again at least 2 years later. Additionally, patients with ≥18 points in MADRS were qualified as depressive. The Fagerström scale for nicotine dependence was administered to smokers. **Results:** Our study shows a relation between severity of depressive symptoms and further deterioration of cognitive functions according to ADAS-cog scale. Regression analysis revealed that smoking associated with severity of depressive disorders is also correlated with the progression of cognitive impairment. **Conclusions:** The results of our study are based on a small number of subjects and should be regarded as early findings. Moreover, nicotine dependency should not be regarded as an isolated factor affecting mood disorders and cognitive impairment progression. Further studies on larger groups of patients and using more sensitive methods of cognitive function assessment are needed.

Keywords: mild cognitive impairment · nicotine dependency · depression

Citation

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Introduction

Tobacco smoking is a very common habit and concerns all age groups [1]. Unfortunately, it is also an important health problem among the elderly [2]. Negative health impact of nicotine use, as well as its positive, though transient, effect on concentration after a one-time exposure to nicotine have been known for many years [3]. On the other hand, relatively little has been known on neurobiological effects of chronic smoking, but the number of studies pointing at a negative impact of tobacco use on numerous aspects of cognitive functioning has significantly increased during the last years. This influence has been observed in all ages and seems to apply to information processing speed and memory functioning at the most [4]. The problems mentioned above can be amplified by deficits which appear as early as in the middle age, e.g. those concerning verbal information memorizing, operational memory, executive functions, the speed of cognitive processes, as well as globally worse results in cognition tests [5-8].

Cognitive deterioration related to chronic smoking is based on brain atrophy which advances faster than in non-smokers [9]. Acceleration of degenerative process is visible in brain neuroimaging [10-11]. Taking the above into consideration, smoking can be regarded as an important risk factor of dementia. This suggestion is confirmed mainly by longitudinal studies aiming at identification of dementia risk factors [12].

Smoking has been associated with a number of psychiatric disorders for a long time now [13-14]. The pathogenesis and course of depressive disorders show a certain correlation with tobacco use [15-16]. Relation between smoking and depression is supposed to apply to various aspects of the disease. Although the influence of nicotine dependence on the development of depression is not usually confirmed, the impact of smoking on intensity of symptoms is much underlined [17]. This includes the correlation between severity of depression and the amount of cigarettes smoked [15]. Such studies pay little attention to the assessment of cognitive functions. Some data suggest the association between smoking and depression may be limited to certain symptoms [18].

Mood disorders also tend to have a significant impact on cognition [19]. One may expect, that this influence may increase with coexistent neurobiologic cause, such as cognitive deterioration associated with ageing [20]. Mood disorders, especially depression, are considered a well-known risk factor for dementia mainly, because they precede its appearance relatively often [21]. However, there is also a reverse correlation. Alzheimer or vascular type histochemical alterations of the brain are known to conduce depressive disorders [22].

Mild cognitive impairment (MCI) is another factor which increases the risk of faster neurocognitive deterioration [23-24]. Despite the progress in research on MCI, there is still controversy regarding the diagnosis, its criteria, range and particularly prognosis. Estimation of cognitive deterioration risk factors, as it is based on available data, shows that patients with a diagnosis of MCI who are smokers and show concurrent depressive symptoms are more susceptible to the development of dementia.

The purpose of this study was to verify the hypothesis stating that cigarette smoking and depression symptoms together are disadvantageous for the prognosis of mild cognitive impairment.

Materials and methods

We recruited the study cohort from among the patients of a single psychiatric outpatient clinic during six consecutive months.

Inclusion criteria for the study:

- informed consent,
- age above 65 years,
- score of 3 (mild cognitive decline) in Global Deterioration Scale (GDS) [25],
- Mini Mental State Examination (MMSE) score of 24 or more [26].

Exclusion criteria for the study:

- diagnosis of dementia regardless of etiology,
- MMSE score below 24,
- Hachinski Ischaemic Scale score 4 or more [27],
- any of the following diseases present at the time of the study or reported by the patient: bipolar disorder, schizophrenia, alcohol dependency, drug or psychoactive substances dependency, epilepsy, Parkinson's disease, mental retardation, consciousness impairment,
- musculoskeletal, auditory or visual impairment during examination which could influence following the directions and procedures in applied clinical scales,
- other serious somatic diseases, particularly in decompensation.

The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and Montgomery-Asberg Depression Rating Scale (MADRS) were performed at inclusion [28-29]. MADRS score of ≥18 qualified the

participant to the group of patients with depressive symptoms. The second assessment with ADAS-cog has been repeated after at least two years.

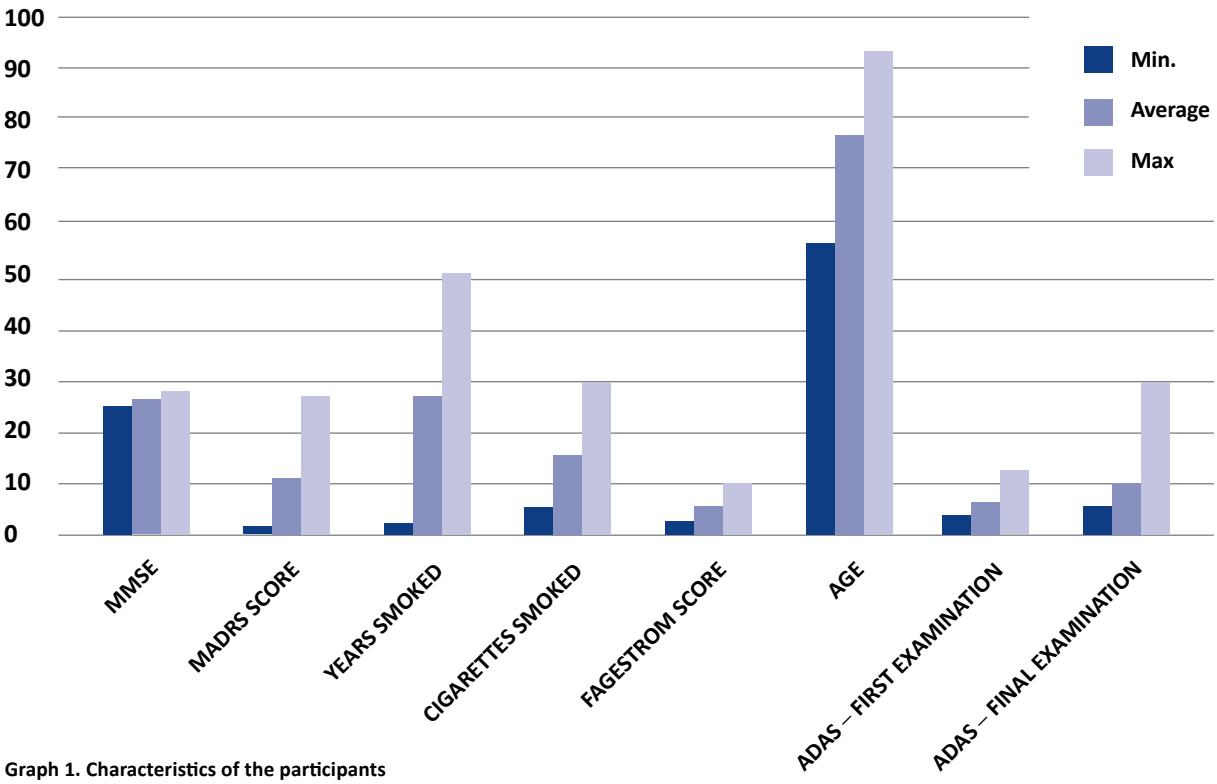
Additionally, to estimate the intensity of tobacco smoking, detailed history was taken from the participant and, if possible, that information was verified by a relative. Specifically, we sought to determine how long the participant has been smoking (in years) and the average amount of cigarettes smoked per day. We qualified the participant as a smoker, if during lifetime he smoked for a period of one year continuously every day, regardless of the number of cigarettes smoked. The participants who were actively smoking also performed the Fagerström Test for Nicotine Dependence [30].

Results were collected on Microsoft Excel 2010 (Microsoft, Redmond, USA). Statistical analysis was performed on Statistica 12.0 (StatSoft Inc./Dell Software, Round Rock, USA). Obtained data was verified statistically by parametric tests (t for two independent means). The predetermined significance level (p value) was 0,05 for all applied statistical tests. Test results for which significance level was ≤ 0,05 were deemed as statistically significant. Two-sided confidence interval was adopted. Multivariate multiple regression was used for further analysis of variables.

Results

Of the initial 1567 patients we screened, 43 were finally included in the study. The ADAS-cog scale was repeated after 24-48 months in 26 participants. The most frequent reason for not administering the scale again was losing contact with participants due to their failure to attend an appointment at the clinic. Sixteen of those participants were qualified as smokers (9 of them as past smokers and 7 as active smokers) and 10 as non-smokers.

For the purpose of the study, only data gathered from participants examined with ADAS-cog scale twice was analyzed (n = 26) (see Graph 1). Our results, despite being based on a small number of participants, show a correlation of depressive symptoms (as an overall MADRS score) and further cognitive decline according to ADAS-cog (see Table 1). There is no proven correlation regarding second of the analyzed factors, smoking. Although comparing past or active smokers with participants who have never smoked seems to show a tendency, it is not statistically relevant (t = -1,42) (see Graph 2). Detailed comparisons with regards to smoking status (past, current and non-smokers) are available in supplementary tables: https://ejtcm.gumed.edu.pl/files/61.



Graph 1. Characteristics of the participants

Note: Years smoked, cigarettes smoked and Fagerstrom score apply to smokers only (N = 16)

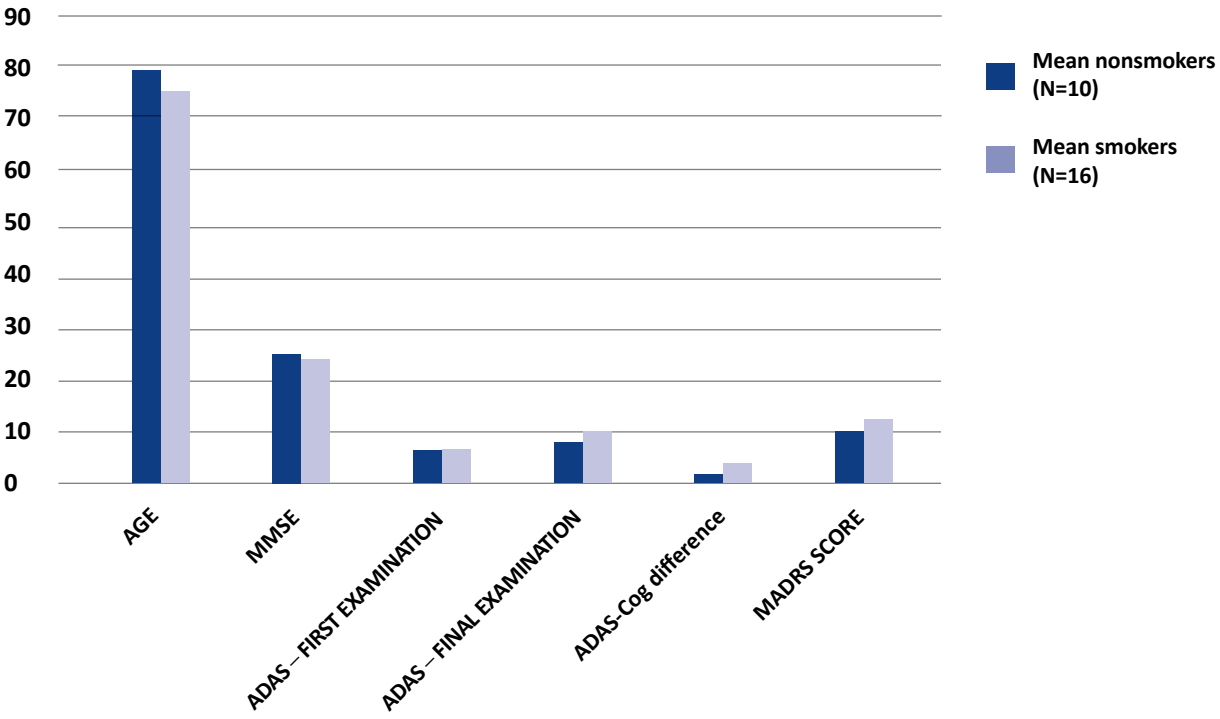
ADAS – Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog);

MMSE – Mini-Mental State Examination; MADRS – Montgomery-Asberg Depression Rating Scale

Table 1. Comparison of subjects with the Montgomery-Asberg Depression Rating Scale (MADRS) scores of < 18 and ≥ 18 points

	Mean MADRS < 18pts (N = 17)	Mean MADRS ≥ 18pts (N = 9)	T	df	P
AGE	75,35	79,55	-0,94	24	0,37
MMSE	25,82	24,33	3,91	24	0,00
ADAS – FIRST EXAMINATION	6,59	8,89	-2,93	24	0,00
ADAS – FINAL EXAMINATION	7,65	13,33	-4,21	24	0,00
Difference in ADAS scale scores (FIRST EXAMINATION – FINAL EXAMINATION)	1,12	4,55	-2,98	24	0,01
MADRS SCORE	6,12	21,55	-9,78	24	0,00

Difference in ADAS scores between first and final examination calculated in points. ADAS – Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog); df – degrees of freedom; MARDS -Montgomery-Asberg Depression Rating Scale; MMSE – Mini-Mental State Examination; N – number of subjects; P – statistical significance; T – random variable



Graph 2. Comparison of non-smokers with smokers (present and past)

Difference in ADAS scale scores between first and final examination calculated in points. P > 0,05 for all results. ADAS – Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog); MADRS – Montgomery-Asberg Depression Rating Scale; MMSE – Mini-Mental State Examination; N – number of subjects

Regression analysis shows a relation between smoking in combination with the severity of depressive disorders and cognitive impairment progression (see Table 2).

Table 2. Multiple regression analysis (dependent variable of ADAS--cog scale difference in points between baseline score and upon follow-up 2 years later)

Independent variables	Beta coefficient
MADRS SCORE	0,777
YEARS SMOKED	-0,09
CIGARETTES SMOKED	0,49
Multiple R = 0,81991809	
F = 8,205008	
SD: 2,248654	
T(12) = 1,3065	
P = 0,2159	

MADRS – Montgomery-Asberg Depression Rating Scale; N – number of subjects; P – statistical significance; SD – standard deviation; T – random variable

Discussion

A variety of data implies that both smoking and depressive disorders show a certain correlation with the rate of cognitive decline [31-32] . It is still a matter of discussion whether these can be viewed as separate factors or if their mutual influences modulate the intensity of impact. Some observations on codependence of cigarette smoking and mood disorders seem to suggest the latter [15, 17]. On the other hand, there are multiple factors behind nicotine dependence or depression, such as some personality predispositions, which in turn can be an outcome of mechanisms associated with neurobiological conditioning of cognitive disorders progress.

It is a fact that both mood disorders and smoking do not always show a correlation with cognitive decline. A symptomatic example is proven lack of influence of smoking in patients with ApoE 4 [33-34]. Although one may expect that an accumulation of a so-called strong risk factor (e.g. ApoE 4) with a potential risk factor (e.g. cigarette smoking) may increase the effect of the latter, this is not the case.

The relation of depression and cognitive functions deterioration has caught a lot of attention, but the mechanism is still not known. One of the hypotheses assumes that depression induces chronic stress dysregulation, which may lead to hippocampal structures damage [35-36]. A major problem in evaluating this occurrence is a great difficulty in differentiating early stages of dementia, which often manifest themselves as mood worsening and other depressive symptoms [37]. This does not diminish the meaning of depression as a risk factor, it may however draw doubt when attempting to establish its role in the pathogenesis of the process. It seems that both disorders (depression and dementia) are a result of the same neurobiological process.

A basis for assessing mood disorders in the examined group was MADRS, which is probably the most commonly used depression scale, instead of the diagnosis of depression according to the classification criteria. This decision was made taking into consideration fact, that depression in elderly patients, especially when coexistent with cognitive disorders, tend to have atypical clinical picture, not compliant with diagnostic criteria. Consequently, ascertaining depressive symptoms is far more often than asserting depressive episode [38].

The concept of 'cigarette smoking' is somewhat imprecise. One needs to realize that cigarette smoke contains around 4000 components, each of them being possibly directly or indirectly harmful to brain functions [39]. Their meaning can differ greatly with regard to many factors including way of smoking, its intensity, period of smoking, age of smoker. Furthermore, particular products from different manufacturers cannot always be compared. Despite the fact that contemporary studies point to an indisputable toxicity of smoking to neurobiological functions and, as a result, to cognition, its mechanism remains in the area of imprecise hypotheses.

Possible mechanisms include direct cytotoxic influence of substances emitted during the process of smoking [40] or possible impact on cognition by generating vascular processes [41] which play a significant role in pathogenesis of dementia – Alzheimer's type or other [42-43]. Moreover people who are not nicoti-

ne dependent develop a short effect of increasing the number of nicotine receptors and transient improvement in certain aspects of attention. At the same time smoking greatly increases oxidative stress which is another important pathogenesis factor, especially in Alzheimer's disease [44-45]. There are various more potential mechanisms of action of substances emitted during smoking. Those that may be worth mentioning are indirect mechanisms such as a variety of adverse metabolic effects which have a doubtless influence on cerebral processes [46-47]. Some data show that cessation of smoking at a certain point during lifetime does not unfortunately neutralize the potentially harmful impact on cognition in old age [48-49].

Results of our study point to this at some extent. Although the very fact of smoking has not been confirmed as a statistically relevant factor of cognitive impairment progression, the application of regression analysis shows that such a relation exists in combination with the severity of depressive disorders (MADRS).

Taking into account the number of participants, our results should be regarded as early findings, which requires confirmation in the future. The validity of results is also limited by the sensitivity of scale used to assess cognitive functions – ADAS-cog. One may have doubts whether it is a precise enough tool in MCI, where the impairment is, by definition, insignificant. Further studies should be based on more sensitive methods of cognitive functions examination. Eventually, the estimation of smoking habits was in a large part imprecise, which must have had an impact on our results. Moreover it should be considered, that obtained results could be influenced by recall bias related to imprecise collection of this data after so many years and not always from the patient himself.

Conclusions

Results, despite being based on a small number of participants, show a relation of depressive symptoms (as an overall MADRS score) to further cognitive decline according to ADAS-cog. With regard to the number of participants, a detailed analysis of particular MADRS items has been abandoned, yet earlier studies imply that a relation here may also exist [38].

There is no proven relation regarding second of the analyzed factors, smoking. Although comparing participants who have never smoked with past or current smokers seems to show a tendency to be statistically relevant (t = -1,42). Taking into consideration the postulated complexity of the impact smoking has on cognitive functions, it comes to no surprise that any possible relation would be relatively vague. Regression analysis shows a correlation between smoking in combination with the severity of depressive disorders and cognitive impairment progression.

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RESEARCH ARTICLE

Costs of elective vs emergency cholecystectomy in diabetic patients

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Abstract

Introduction: Hospitalization costs of diabetic patients are estimated to be higher than non-diabetic. Literature on the topic is however limited. The aim of this study was to compare the costs of elective and emergency cholecystectomy of diabetic and non-diabetic patients. **Material and methods:** A retrospective analysis involved diabetic versus non-diabetic age- and sex-matched patients who underwent emergency and elective cholecystectomy at a single center in Poland between 2016-2019. **Results:** The total costs of an elective cholecystectomy were 739.31 ± 423.07 USD for diabetic patients and 797.14 ± 772.24 USD for non-diabetic patients ($p = 0.51$). Whereas emergency cholecystectomy total costs were 3950.72 ± 2856.83 USD (diabetic patients) and 2464.31 ± 1718.21 USD (non-diabetic patients) ($p = 0.04$). The difference in total costs between elective cholecystectomy vs emergency cholecystectomy in both groups (diabetic vs non-diabetic patients) was statistically significant ($p < 0.01$ vs $p < 0.05$ respectively). **Conclusions:** In this study we demonstrated that emergency cholecystectomy is associated with a significant increase in hospitalization costs, particularly in diabetic patients. This suggests that early qualification of diabetic patients for an elective cholecystectomy could be beneficial for both diabetic patients and public health insurers.

Keywords: diabetes · elective cholecystectomy · emergency cholecystectomy · costs of hospitalization

Citation

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Introduction

According to the latest World Health Organization data, the estimated number of people suffering from diabetes worldwide is 422 million and the incidence of diabetes is increasing rapidly [1]. Because of its many complications, diabetes mellitus is associated with significant costs in public healthcare systems around the globe [2,3]. Acute cholecystitis in diabetic patients is often complicated by gangrenous cholecystitis [1], peritonitis, preoperative perforation, impaired wound healing, infections, increased risk of cardiovascular events and renal failure [4–11]. For this reason, diabetic patients hospitalisation costs are estimated to be higher than non-diabetic. Literature on the topic is limited and mostly concludes that immediate intervention leads to a decrease in costs and shortens the length of hospital stay [12–16]. The aim of this study was to compare the costs of elective and emergency cholecystectomy of diabetic and non-diabetic patients.

Materials and methods

A retrospective analysis involved patients who underwent emergency and elective cholecystectomy at the Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdańsk (Poland) between 2016 and 2019. Patients were assigned to diabetic group whenever diabetes mellitus of any type was identified in admission work-up. Using institutional registries we identified a total of 661 patients who underwent emergency cholecystectomy, of whom 70 patients had diabetes and 591 were non-diabetic. A random sample of 16 diabetic patients was included to the study depending on admission data criteria and was used to assign an age- and sex-adjusted control group.

A total of 1608 patients who underwent elective cholecystectomy where identified in institutional registries, of whom 135 had diabetes and 1473 were non-diabetic patients. A random sample of 20 diabetic patients were included to the study depending on admission data criteria. The control group of 80 patients was age- and sex-matched in a 4:1 ratio (Non-diabetic: Diabetic) (see Figure 1, Table 1).

The following were the criteria of inclusion into the study: unplanned or planned admission depending on group, cholecystectomy performed within 72 h of admission, and the availability of complete report of hospitalization costs in the electronic system. Patients were assigned to the diabetic group whenever diabetes mellitus of any type was identified in the admission work-up. The exclusion criteria included the lack of data on the costs of hospitalization, incomplete

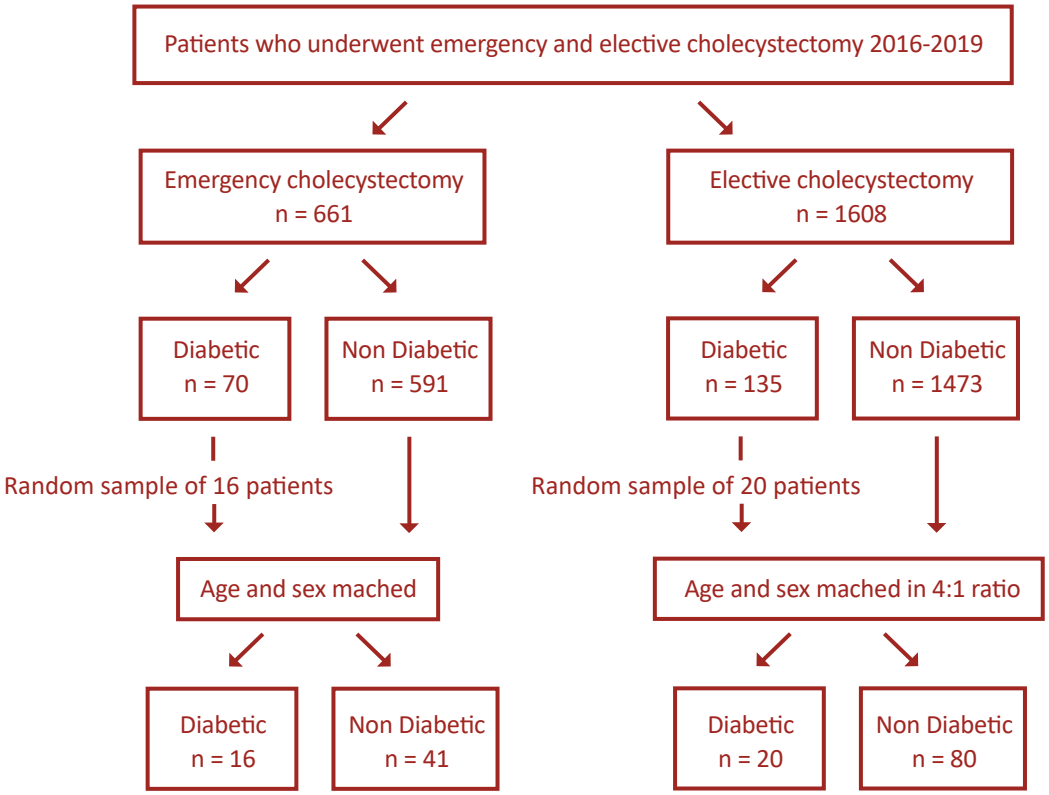

Figure 1. Flowchart illustrating patient selection

Table 1. Age distribution of patients in the emergency vs elective cholecystectomy group

Age	Diabetic	Non-diabetic	Diabetic	Non-diabetic
> 40	1	5	1	6
41-60	7	16	11	44
61-80	7	15	8	30
> 80	1	5	0	0

data on time or course of hospitalization, more than one surgery performed that was not related to cholecystectomy and its complications during the same hospitalization, cholecystectomy performed during hospitalization for a different reason.

Calculation of the direct costs of the Emergency Department included: medical imaging, medicines, consultations, laboratory tests, procedures performed and equipment. Whereas the General Surgery Department costs taken into account (in emergency and elective cholecystectomy) were: medical imaging, medicines, consultations, histopathology, laboratory works, procedures performed, equipment, operating room cost, cost of stay. Total costs of emergency cholecystectomy were a sum of costs incurred at the Emergency and General Surgery Departments. Total hospitalization costs taken into account for elective cholecystectomy were all generated at the General Surgery Department. Costs were converted from Polish Złoty (PLN) to US Dollars (USD) using the National Bank of Poland exchange rates from 11 September 2019. Descriptive analysis included medians, means and standard deviations. In comparative analysis U Mann-Whitney test, Student's t-test and the X^2 test were used. Distribution was tested using Shapiro-Wilk test. Statistical significance was accepted at $p < 0.05$. Statistical analyses were performed using Statistica 13.3 (TIBCO Software, Palo Alto, United States).

Results

A group of 57 patients (16 with diabetes and 41 non-diabetic) who underwent emergency cholecystectomy was analyzed. A total of 100 patients who underwent elective cholecystectomy were included to the study, 20 patients with diabetes and 80 patients without. Patients were matched in the group by age and sex. In the emergency group the access to viable data from the point of admission was limited, and therefore group size was limited as well. The downgrading of data quality was ruled out by the mean group size.

Total hospitalization cost

In a group of patients who underwent elective cholecystectomy, the total costs for diabetic patients were 739.31 ± 423.07 USD [median: 536.15 USD; range: 287.20 USD – 1606.67 USD] and for non-diabetic was 797.14 ± 772.24 USD ($p = 0.51$) [median: 651.47 USD; range: 281.75 – 6089.41 USD]. In a group of patients who underwent emergency cholecystectomy total costs for diabetic patients were 3950.72 ± 2856.83 USD [median: 3188.67 USD; range: 753.23 – 10760.15 USD] and 2464.31 ± 1718.21 USD ($p = 0.04$) [median: 2087.56 USD; range: 689.26 USD – 10950.16 USD] for non-diabetic patients. The difference in total costs between elective cholecystectomy and emergency cholecystectomy in both groups (diabetic and non-diabetic patients) was statistically significant ($p < 0.01$, $p < 0.05$ respectively) (see Table 2 and Table 3).

Table 2. Mean emergency ward costs in emergency cholecystectomy group

	Diabetic	Non-diabetic	p-value
Medical imaging	79.52 USD	50.29 USD	0.495
Consultations	31.13 USD	23.55 USD	0.356
Procedures	32.64 USD	35.33 USD	0.670
Laboratory tests	23.24 USD	20.91 USD	0.477
Medicines	3.47 USD	4.88USD	0.279
Equipment	8.35 USD	6.12 USD	0.657
Other	0 USD	0 USD	0.000
Total*	178.48 USD	141.20 USD	0.505

***Due to the applied approximations, individual costs cannot be summed up to a total cost.**

Table 3. Mean general surgery ward costs in emergency vs planned cholecystectomy group

	Diabetic	Non-diabetic	p-value	Diabetic	Non-diabetic	p-value
Cost of stay	1416.86 USD	758.01 USD	0.015	329.19 USD	424.29 USD	0.829
Operation room	628.81 USD	577.49 USD	0.676	605.53 USD	566.15 USD	0.113
Histopathology	31.56 USD	11.24 USD	0.901	9.40 USD	11.05 USD	0.595
Laboratory tests	73.86 USD	29.13 USD	0.012	11.96 USD	15.14 USD	0.510
Medicines	371.23 USD	178.93 USD	0.083	17.42 USD	34.10 USD	0.561
Medical imaging	87.28 USD	34.47 USD	0.066	0 USD	0 USD	0.000
Equipment	252.53 USD	98.09 USD	0.001	61.44 USD	63.59 USD	0.638
Consultations	26.36 USD	12.02 USD	0.050	0 USD	0 USD	0.000
Other	68.02 USD	18.50 USD	0.038	0 USD	0 USD	0.000
Total hospitalization*	3950.72 USD	2464.31 USD	0.040	739.31 USD	797.14 USD	0.515

***Due to the applied approximations, individual costs cannot be summed up to a total cost.**

Procedure-related costs

Procedure-related costs included General Surgery Department procedures plus costs of operating theatre (Table 3). Procedure costs in the emergency group were 724.60 ± 416.92 USD for diabetic patients and 625.26 ± 304.78 USD for non-diabetic patients (p = 0.613). Elective cholecystectomy group costs were 605.53 ± 246.04 USD for diabetic patients and 566.15 ± 325.37 USD for non-diabetic patients, p = 0.113. Differences in procedural costs between patients in diabetic and non-diabetic groups undergoing emergency cholecystectomy and those who underwent planned cholecystectomy were not statistically-significant, p = 0.824 and p = 0,992 respectively.

Other costs

Medical imaging costs were only applicable to the emergency cholecystectomy group and at the General Surgery Department they were 87.28 ± 152.21 USD for diabetic patients and 34.47 ± 70.87 USD for non-diabetic patients, p = 0,066. Whereas at the Emergency Department they were 79.52 ± 103.90 USD for diabetic patients and 50.29 ± 75.10 USD for non-diabetic, p = 0495. Other types of costs were not statistically significant with all p-values greater than 0.05 (see Table 2 and Table 3).

Length of stay

Mean length of stay counted in days for patients undergoing elective surgery was: 3.12 ± 2.96 for diabetic patients and 2.35 ± 0.87 for non-diabetic patients, (p = 0.555). Difference between elective and emergency cholecystectomy was statistically significant both for diabetic p < 0.001 and for non-diabetic patients p < 0.001. For emergency cholecystectomy mean length of stay was 10.62 ± 8.15 for diabetics and 5.49 ± 3.96 for non-diabetic patients p = 0.017).

Discussion

To our knowledge, this is the first report of specific hospitalization costs of diabetic and non-diabetic patients undergoing elective and emergency cholecystectomy. Our results suggest that emergent intervention in diabetic and non-diabetic group of patients leads to greater total costs of hospitalization,

costs of stay and procedure-related costs compared to planned cholecystectomy ($p < 0.05$). Furthermore, a significant difference between emergency hospitalization costs of diabetic and non-diabetic patients was found ($p = 0.04$), while there was no significant difference in cost between diabetic and non-diabetic patients in elective hospitalisation (see Table 3). This suggests that acute cholecystitis is not only burdened with higher risk of complications but also with a much higher cost. This may be another important factor underlining the need for diabetes patients to undergo elective surgery. However according to EASL guidelines, routine surgical treatment is not recommended for patients with asymptomatic gallbladder stones [17]. In our analysis the costs of hospitalisation were greater in emergency intervention both in diabetic and non-diabetic patients. It was reported numerous times, that elective surgery carries lower risk of complications [12,15,18,19]. Perhaps this is due to the fact that patients undergoing elective surgery not only do not have a fast progressing emergency condition but also are better prepared for surgery i.e. intentional weight loss, adequate glycemic control, appropriate treatment of possible arrhythmias and hypertension. [20]

Treatment of complications significantly prolong the hospital stay directly leading to increased costs of hospitalization. Costs of emergency surgery in diabetic patients are significantly higher ($p = 0.015$) than in non-diabetic. This is due to increased levels of complications intraoperatively and in postoperative period in diabetic patients with acute cholecystitis in comparison to-non diabetics [11,19,21–24].

Increase of procedure-related costs could be explained by frequently more advanced disease at admission of diabetic patients with acute cholecystitis. As reported previously, diabetics more often present with gangrenous cholecystitis, gall bladder perforation or emphysematous cholecystitis [1,7,25–28]. This leads to extended duration of surgery and increased use of materials during surgical interventions resulting in increased costs of surgery [29]. Increased rate of complications such as wound infections or impaired wound healing requires additional instrumental interventions during post-operative stay and thus generates further costs [30,31].

Imaging costs were a significant part of increased costs in emergency patients because in our study patients undergoing elective cholecystectomy obtained imaging prior to their admission Furthermore, medical imaging during hospital stay was required due to emerging complications. It can be considered one of the major cost-generating factors along with procedures and the length of stay.

In our study, the length of hospitalization is a measure of effectiveness. There is a statistically significant difference between the length of hospitalization of elective and emergency patients in both groups diabetic and non-diabetic ($p < 0.001$) and the emergency patients' length of stay was longer.

There is no significant difference between the length of stay of diabetic and non-diabetic patients undergoing elective surgery. This is in contrast to emergency procedures. The length of stay of patients with diabetes operated urgently was statistically significantly longer than in non-diabetic patients (10.62 ± 8.15 vs 5.49 ± 3.96, $p = 0.017$). This may be due to a more locally advanced disease and more common complications. Regardless of the reason above, our study clearly shows that diabetic patients may benefit from elective cholecystectomy.

Study limitations

First of all, this study is limited due to its retrospective nature. We performed a univariate analysis and did not involve potential cofactors such as glycaemia control, comorbidities and medications. Furthermore, the calculated costs might differ in other health care systems and crude values might vary substantially. However, we believe that the differences shown seem universal due to common cost-generating factors.

Conclusion

In this study we demonstrated that an emergency cholecystectomy in a diabetic patient is associated with greater costs when compared to a planned cholecystectomy. While there are no differences in the costs of elective hospitalizations, there is a statistically significant difference in the costs of emergency surgery between diabetic and non-diabetic patients. As cholelithiasis in diabetic patients can often be diagnosed at its asymptomatic stage, we suggest that qualifying these patients to an elective cholecystectomy early on may lead to fewer serious complications and a decrease in total costs of hospitalization. Although elective cholecystectomy is not supported in current guidelines, it seems that such approach could be beneficial for both diabetic patients and public health insurers. (European Association for the Study of the Liver (EASL), 2016)

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RESEARCH ARTICLE

Panoramic radiograph – a useful tool to assess the difficulty in extraction of third molars

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Abstract

Introduction: Third molars (TMs) are the most frequently impacted teeth due to the frequent lack of space in the dental arch resulting in their malposition or inability to erupt. Partially erupted TMs that cause recurrent inflammatory conditions must be removed. The aim of this study was to assess TM position on panoramic radiographs. **Materials and methods:** We evaluated 200 panoramic radiographs of patients 18-72 years of age. Teeth were assessed in terms of the presence of dental follicle, cervix/root ratio and root development stage. Maxillary TMs were assessed using the Archer and Pell and Gregory classifications, whereas the mandibular ones according to Pell and Gregory, Winter, IAN and Pederson classifications. **Results:** 622 TMs were assessed. In the maxilla, the most common type was A-positioned, vertically angulated TM with completely formed root/roots. In the mandible, the most common type was A1-positioned, mesioangular TM with completely formed root/roots and without enlarged follicle. According to Pederson's index, 59.44% TMs were moderately difficult to extract. Most roots were in contact with inferior alveolar nerve. **Conclusions:** The use of the classifications mentioned above is helpful in assessment of the surgery difficulty level. In the long term this allows to increase the predictability of the procedure and minimize the intra- and post-operative complications.

Keywords: Archer classification · Pell and Gregory classification · IAN classification · Pederson scale · Winter classification

Citation

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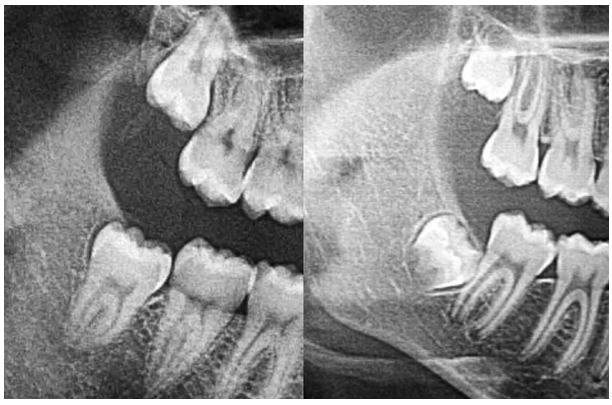
Introduction

Third molars (TMs) are the most frequently impacted teeth due to the frequent lack of space in the dental arch results in their malposition or inability to erupt. This promotes pericoronitis (operculitis), root resorption in second molars, dental caries, pulpitis, periodontitis, osteitis or ulcerative stomatitis. For these and other reasons the TMs often have to be extracted. The pantomographic radiograph is a basic tool used to evaluate the position of the TMs before the procedure [1-3]. The aim of this paper was to evaluate the TMs on panoramic radiographs using selected indicators.

Materials and methods

The study group included 200 patients, 18-72 years of age, who were treated at a single instutution in Gdańsk (Poland) in the years 2018-2019. The inclusion criteria were: having at least one TM, lack of chronic diseases, not taking any medication. Informed consent was obtained from all the participants and their anonymity was preserved.

Teeth were assessed in terms of the root formation stage (complete or incomplete root development; Fig. 1), cervix/root ratio (roots spaced more widely than the cervix, cervix diameter larger than the width of the roots or width of the roots equal to the diameter of the cervix; Fig. 2) and occurrence of enlarged follicle (Fig. 3). Upper teeth were assessed using the Archer (Fig. 4) and Pell and Gregory classification (Fig. 5). The relation of the lower TMs to the inferior alveolar nerve was assessed using the IAN (inferior alveolar nerve) classification (Fig. 6). Teeth angulation was assessed using the Winter (Fig. 7) and the Pell and Gregory classifications (Fig. 8 and 9), as well as the Pederson index (Table 1) [4-14].



1A **1B**

Figure 1. Roots development (lower third molars – right side) A. complete; B. incomplete roots development

Table 1. Difficulty level prediction for impacted mandibular third molar removal – Pederson scale

Classification	Score
Spatial relationship	
Mesioangular	1
Horizontal/ transverse	2
Vertical	3
Distoangular	4
Depth	
Level A	1
Level B	2
Level C	3
Ramus relationship	
Class I	1
Class II	2
Class III	3
Difficulty index	
Very difficult	**7-10**
Moderately difficult	**5-6**
Minimally difficult	**3-4**

TM – third molar; level A – the occlusal plane of the TM is at the same level as the occlusal plane of the second molar; level B – the occlusal plane of the TM is between the occlusal plane and the cervical margin of the second molar; level C – the occlusal level of the TM is below the cervical margin of the second molar; class I – there is sufficient amount of space between the anterior border of the ramus and the distal part of the second molar for the mesiodistal diameter of the TM crown; class II – the space between the anterior border of the ramus and the distal part of the second molar is less than the mesio-distal diameter of the TM crown; class III – most part or all of the TM is located within the ramus

Figure 2. Cervix/root ratio (lower third molars – right side)
A. cervix diameter larger than the width of the roots; B. width of the roots equal to the diameter of the cervix; C. roots spaced more widely than the cervix

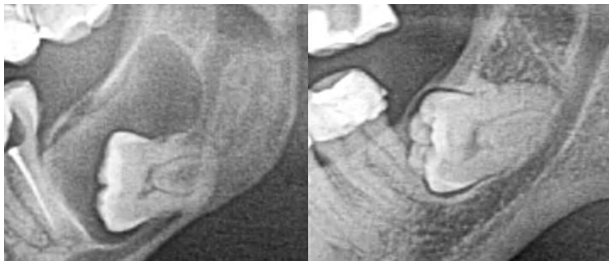


Figure 3. Dental follicle (lower third molars – left side)
A. enlarged follicle; B. non-enlarged follicle

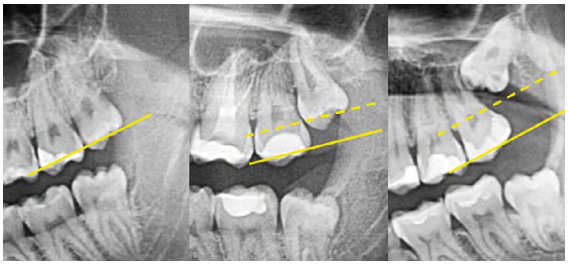


Figure 5. Pell and Gregory classification for the maxilla (upper third molars – left side)
A. level A; B. level B; C. level C

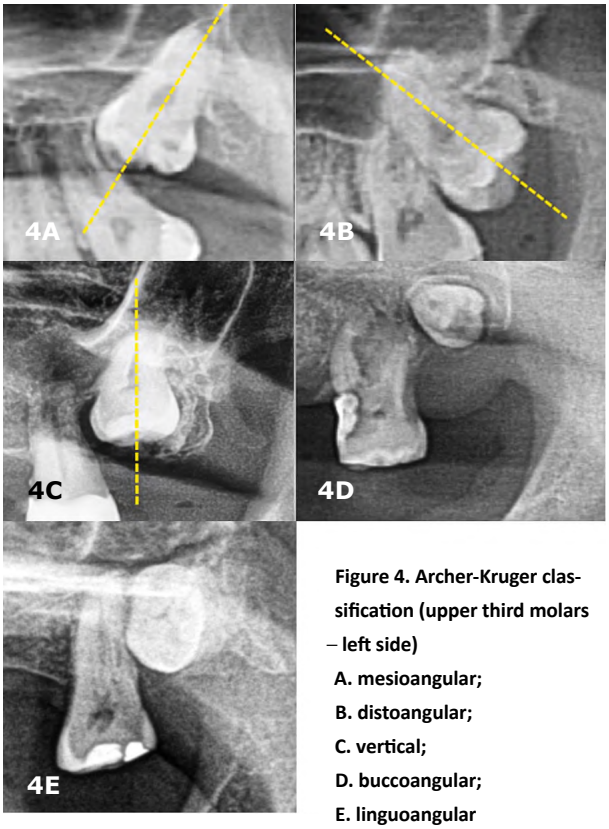


Figure 4. Archer-Kruger classification (upper third molars – left side)
A. mesioangular;
B. distoangular;
C. vertical;
D. buccoangular;
E. linguoangular

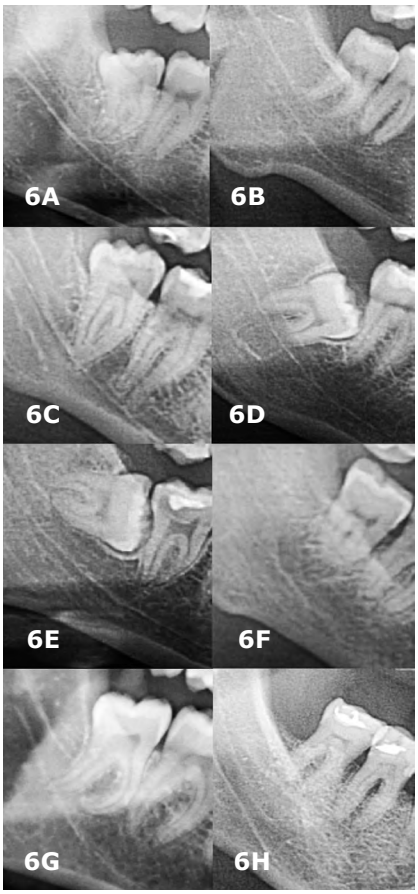


Figure 6. IAN classification (lower third molars – right side)
A. darkening of roots; B. deflection of roots; C. narrowing of roots; D. dark and bifid apex of roots; E. interruption of white line of the canal; F. diversion of canal; G. narrowing of the canal; H. no relationship

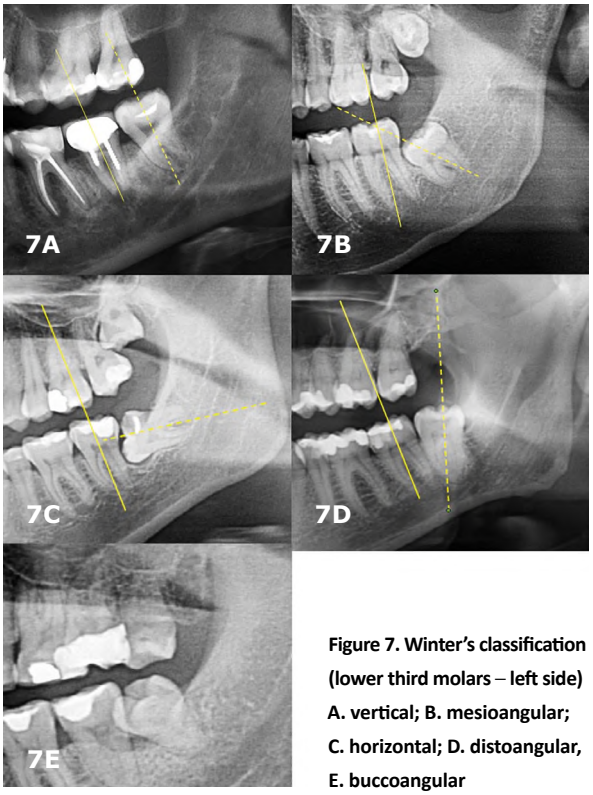


Figure 7. Winter's classification (lower third molars – left side) A. vertical; B. mesioangular; C. horizontal; D. distoangular, E. buccoangular

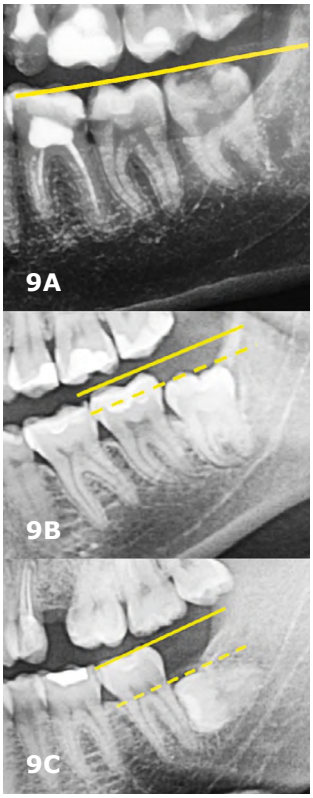


Figure 9. Pell and Gregory classification for the mandible (lower third molars – left side) A. level A; B. level B; C. level C

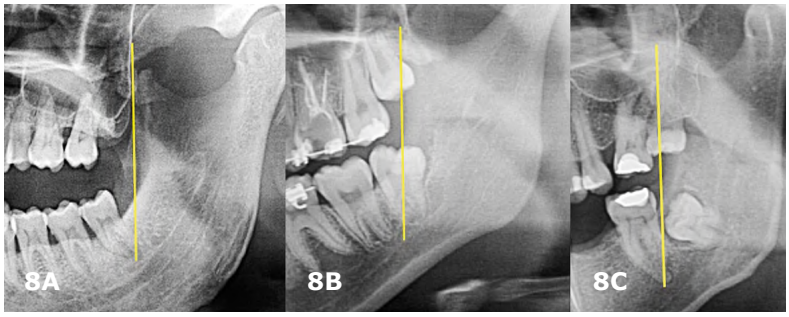


Figure 8. Pell and Gregory classification for the mandible (lower third molars – left side) A. class I; B. class II; C. class III

Statistical analysis was performed using the STATISTICA 13.3 (StatSoft Inc. Tulsa, United States) licensed by the Medical University of Gdańsk. All tests were considered statistically significant at $p \leq 0.05$. Normal distribution of the analysed variables was verified with the Shapiro-Wilk test. Non-parametric tests were used to evaluate the scales (Mann-Whitney, Wilcoxon and Spearman correlation tests).

Results

Of the total evaluated 622 TMs, 299 were in the maxilla and 323 in the mandible. In the maxilla, most TMs were type A according to the Pell and Gregory classification (n = 158; 52.84%), vertically angulated (n = 210; 70.23%) according to the Archer classification and with complete root formation (n = 216; 72.24%; Table 2 and 3). Whereas in the mandible most TMs were type A1 (n = 143; 44.30%), mesioangular (n = 164; 50.77%), with complete root development (n = 248; 76.80%) and without enlarged follicle (n = 274; 84.83%). Most roots (61.99%) were in contact with the inferior alveolar nerve (IAN classification) and the most common type was the one with dark and bifid apices. According to Pederson's scale, 59.44% of the TMs were moderately difficult to remove. Pederson's scale identified significant differences within the Pell and Gregory classification (position A1 significantly differs from A2, C2, B2, C3 and C1 ones). Evaluating the median within individual groups, it can be shown that the molars with the most difficulty (according to Pederson scale) belonged to C3, B3 and A3 groups; followed by B2, C2, A2 and C1, B1, A1 (Tables 2 and 4).

Table 2. Assessment of root development and enlarged follicle of third molars

Classification	Maxilla		Mandible		Total	
	n	%	n	%	n	%
Root development						
Complete root development	216	72.24	248	76.80	464	74.60
Incomplete root development	83	27.76	75	23.20	158	25.40
Enlarged follicle						
Yes	0	0	49	15.17	49	7.88
No	299	100.0	274	84.83	573	92.12

Table 3. Assessment of third molars in the maxilla

Classification	Maxilla	
	n	%
Archer and Kruger classification		
Mesioangular	26	8.70
Distoangular	39	13.04
Vertical	210	70.23
Horizontal	1	0.33
Buccoangular	21	7.02
Linguoangular	2	0.67
Inverted	0	0
Pell-Gregory classification		
Level A	158	52.84
Level B	38	12.71
Level C	103	34.45

TM – third molar; level A – the occlusal plane of the TM is at the same level as the occlusal plane of the second molar; level B – the occlusal plane of the TM is between the occlusal plane and the cervical margin of the second molar; level C – the occlusal level of the TM is below the cervical margin of the second molar

The studied population of patients was not normally distributed (Shapiro-Wilk's test). The Spearman-rank correlation coefficient revealed a relationship between the higher scores in the Pederson scale and the IAN classification, complete root development and roots spaced more widely than the cervix. The more complicated and difficult the position according to the Pederson scale, the higher the risk of the inferior alveolar nerve injury. The relationship between the complete root development and the Pearson index indicates that it is more difficult to remove the tooth with completely formed roots and with roots spaced more widely than the cervix.

Discussion

The stage of root development is of significance during the TM extraction procedure. The root formation process may be classified as complete or incomplete. It is assumed that the shorter the roots, the easier the extraction. Roots spaced more widely than the cervix suggest more difficulties during procedure when compared with more tapered roots. Enlarged follicle may facilitate tooth extraction [4-14]. The Archer classification is based on the analysis of the inclination of the long axis of the TM to the second molar in the maxilla. This classification features mesioangular, distoangular, vertical, horizontal, buccoangular, linguoangular and inverted positions. Similarly, Winter's classification is based on the analysis of the inclination of the long axis of the TM to the second molar in the mandible and features mesioangular, distoangular, vertical, horizontal, buccoangular, linguoangular and inverted positions [9-10]. Neither of these two classifications includes the assessment of the TM relation to the occlusal plane (Archer and Winter classifications) and the Winter classification doesn't take cognisance of the relation of the TM to the ramus of the mandible. The Pell and Gregory index supplements Winter and Archer's shortcomings by evaluating the TM rela-

Table 4. Assessment of third molars in the mandible

Classification	Maxilla	
	n	%
Cervix/root ratio		
Roots spaced more widely than the cervix	116	35.84
Cervix diameter larger than the roots	76	23.53
Width of the roots equal to the diameter of the cervix	111	34.30
Less than 50% of the root is formed – impossible assessment	20	6.33
Winter classification (for mandible)		
Mesioangular	164	50.77
Distoangular	97	30.03
Vertical	29	8.98
Horizontal	16	4.95
Buccoangular	16	4.95
Linguoangular	1	0.31
Inverted	0	0
Pell-Gregory classification		
Level A	189	58.51
Level B	71	21.98
Level C	63	19.50
Class 1	182	56.35
Class 2	119	36.84
Class 3	22	6.81
A1	143	44.27
A2	43	13.31
A3	3	0.93
B1	27	8.35

Classification	Maxilla	
	n	%
Pell-Gregory classification		
B2	41	12.69
B3	3	0.93
C1	12	3.72
C2	35	10.84
C3	16	4.95
The TM in relation to inferior alveolar nerve		
Darkening of roots	26	8.05
Deflection of roots	24	7.43
Narrowing of roots	7	2.17
Dark and bifid apex of roots	86	23.63
Interruption of white line of canal	28	8.67
Diversion of canal	20	6.19
Narrowing of canal	6	1.86
No relation with canal	126	39.01
Pederson classification		
Very difficult	72	22.29
Moderately difficult	192	59.44
Minimally difficult	59	18.27

TM – third molar; level A – the occlusal plane of the TM is at the same level as the occlusal plane of the second molar; level B – the occlusal plane of the TM is between the occlusal plane and the cervical margin of the second molar; level C – the occlusal level of the TM is below the cervical margin of the second molar; class I – there is sufficient amount of space between the anterior border of the ramus and the distal part of the second molar for the mesiodistal diameter of the TM crown; class II – the space between the anterior border of the ramus and the distal part of the second molar is less than the mesio-distal diameter of the TM crown; class III – most part or all of the TM is located within the ramus

tionship to the occlusal surface of the adjacent second molar and to the anterior border of the ramus of the mandible. In the maxilla, the Pell and Gregory classification evaluates only the relationship to the occlusal surface of the adjacent second molar and the assessment is analogous to the one in the mandible. The IAN classification allows to predict the possible alveolar nerve injury, based on a pantomographic examination. Darkening, deflection or narrowing of roots, dark and bifid apices, interruption of white line of the canal as well as diversion or narrowing of the canal are associated with the risk of postsurgical paraesthesia [4-9].

Several studies suggest that some local and general factors can influence the degree of difficulty associated with the surgical TM removal [10-11, 15-19]. Factors and features contributing to the facilitation of TM removal include: mesioangular impaction, class I and level A according to the Pell and Gregory classification, fused roots that are not in contact with the mandibular canal, incomplete impaction, tapered roots at no point spaced more widely that the diameter at the level of the cervix, incomplete root development, large dental follicle, wide periodontal ligament space and high elastic modulus of the bone. The last two features are more commonly present in younger patients [10-11, 15-19]. Factors and features rendering the extraction procedure difficult are: distoangular impaction, class III and level C according to Pell and Gregory classification, curved roots, complete impaction, roots spaced more widely than the cervix, TM in contact with the second molar or in close proximity to the mandibular canal, complete root development, narrow dental follicle, narrow periodontal ligament space and low elastic modulus of bone. Narrow periodontal ligament space and lower elastic modulus of bone are common in elderly patients [10-11, 15-19].

Yuasa et al. distinguished nine factors that may be of clinical significance while removing a TM (depth, abnormal root curvature, width of roots, number of roots, ramus relationship/space available, proximity to the mandibular canal, periodontal membrane space, relative horizontal position of the third molar) and examined them using univariate and multivariate analysis [12]. Depth, ramus relationship/space available and width of root had impact on the degree of difficulty associated with the surgery. Abnormal root curvature and relative horizontal position of the third molar were not statistically significant [12].

Carvalho et al. emphasized that patient's sex, age or BMI index do not affect the degree of difficulty. However, age does play a role in the event of postoperative complications [15]. Eyricha et al. analysed retrospectively cone beam computed tomography scans performed before the TMs extractions and demonstrated that the two independent factors leading to the postoperative impairment of the inferior alveolar nerve function are narrowing of the IAN canal and direct contact between the IAN and the root [20].

Conclusions

The above- mentioned classifications are useful when assessing the degree of difficulty associated with the TM extraction surgery. In the long term, such an assessment may increase the predictability of the procedure and to minimize the intra- and post-operative complications. All of the described classifications have limitations due to the fact that they do not take into account all the significant features of TMs. In order to evaluate the risk of the intra- and post-operative complications and to plan the procedure properly, all the classifications mentioned above should be taken into account prior to the surgery.

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REVIEW ARTICLE

Changing paradigms in breast cancer treatment

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Abstract

In only the past century, the landscape of breast cancer treatment has completely changed. The Halstedian hypothesis of the "contiguous spread" of breast cancer has been replaced by a consideration of its systemic nature. Today, patients with early-stage breast cancer are managed with breast-conserving therapy, which is as effective as mastectomy. Sentinel lymph node biopsy has largely replaced axillary lymph node dissection. Post-operative radiotherapy, chemotherapy and endocrine therapy have increased survival. Pre-operative cytotoxic therapy allows for less extensive surgery and for a curative resection even in more advanced stages. Rapid progress in molecular oncology revealed a large heterogeneity of breast cancer, resulting in a more personalized approach. Targeted therapies directed against epidermal growth factor receptor type 2 (HER2) have improved survival in HER2-positive breast cancer, which was once a poor-prognosis entity. Multi-gene prognostic signatures better predict prognosis and allow many patients to avoid chemotherapy. Personalized treatment has resulted in decreased toxicity and an improved quality of life. Within the past decades, breast cancer has become a good-prognosis malignancy with a five-year survival in the range of 80-85%. Future development of personalized medicine may further refine treatment based on the tumor's molecular features.

Keywords: breast cancer · sentinel node biopsy · breast-conserving surgery · targeted therapy · molecular profiles

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Introduction

Breast cancer is the most common female malignancy worldwide and is the leading cause of cancer death, accounting for 24.2% of the total cancer cases and 15.5% of cancer deaths in women [1]. Once a virtually incurable entity, it is now considered a good-prognosis malignancy with an 80-85% five-year survival. This spectacular achievement is a result of a better understanding of this tumor's biology, early detection and diagnosis, and progress in treatment. Over the past century, the management of breast cancer has undergone fundamental evolution which not only has resulted in better clinical outcomes, but has also allowed for satisfactory patient survival. This article will outline important milestones and the changing paradigms of breast cancer treatment.

From radical mastectomy to breast conserving therapy

On May 8, 1907, William S. Halsted, a Johns Hopkins University surgeon, declared at the American Surgical Association conference that "breast cancer follows a predictable pattern of spread from one to the next echelon" and that "(a)n en bloc removal of all echelons could thus achieve a cure." With this assumption, he proposed a drastic and disfiguring procedure in which the entire breast, pectoral muscles and axillary lymph nodes were removed. This therapy initiated the so-called "Halstedian era" of breast cancer treatment and radical mastectomy became the standard management for more than half of the 20th century [2]. Although radical mastectomy was widely adopted, surgeons were searching for new solutions. As early as the 1930s, David Patey from London modified Halsted's operation by saving the pectoralis major muscle. This type of surgery was less traumatic and reduced the risk of postoperative complications, e.g. post-mastectomy pain syndrome, lymphedema and a reduced range of motion in the upper limb. To the contrary, there were also attempts to extend breast cancer surgery with a so-called supraradical mastectomy, including the chest wall, internal mammary lymph nodes or even the supraclavicular and mediastinal nodes. These procedures, however, were associated with significant morbidity and no clinical benefit [2].

The major treatment paradigm shift began in the 1960s, when another American surgeon, Bernard Fisher, presented his theory of the systemic nature of breast cancer. As opposed to Halsted's theory of locoregional spread, he argued that women suffering from breast cancer die due to metastatic disease. Hence, surgery may be less extensive, and should be supplemented by systemic therapy to combat micrometastases and reduce the risk of tumor dissemination [3]. Fisher and his colleagues from the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) initiated an era of optimized surgical approaches and systemic adjunctive therapies that were based on randomized clinical trials (RCTs) rather than on empirical grounds.

In the 1970s, the researchers at the NSABP conducted a randomized three-arm trial comparing radical mastectomy to a total (also referred to as "simple") mastectomy (removal of the breast tissue, areola, nipple and skin without axillary dissection), the latter with or without regional irradiation [4]. Axillary dissection was performed only if the lymph nodes became subsequently positive. After 10 years, there was no significant survival difference between the two groups. Consequently, a modified radical mastectomy, sparing the pectoralis major muscle, became the new standard in the 1980s [2]. The next breakthrough in breast cancer surgery was the B-06 clinical trial initiated in the 1970s also by the NSABP [5]. This time, the reasearchers compared the efficacy of total mastectomy and breast conserving surgery (BCS), which included removal of the tumor with surrounding breast tissue. Overall survival (OS) was comparable in both approaches, however the disease-free survival (DFS) was highly improved among patients managed with BCS thanks to the post-operative radiotherapy. At the same time, Umberto Veronesi from the Istituto Tumori di Milano (Italy) published an RCT comparing radical mastectomy and quadrantectomy, another form of BCS [6]. His study supported the paradigm shift from a maximum tolerated surgery to a minimal effective surgery. These results led the National Institutes of Health (NIH; USA) to recommend BCS followed by whole breast radiotherapy as a new standard management in early-stage breast cancer in 1990. Later results of the NSABP and Italian studies confirmed the durable efficacy of breast-saving approaches and established their role in routine practice [7-8].

Avoiding axillary lymphadenectomy

Despite the shortcomings of the "predictable spread" theory of breast cancer, Halstead was not entirely wrong. Indeed, in more than 90% of cases the disease spreads in a predictable manner from level-I through level-II to level-III axillary lymph nodes. After almost a century, his theory resulted in the concept of the sentinel lymph node biopsy (SLNB).

A sentinel lymph node (SLN) is defined as the initial lymph node to which cancer is most likely to spread from the primary tumor. Axillary lymph node dissection (ALND) has long been considered a routine part of breast cancer management, because clinical examination was unreliable for detection of axillary involvement. However, ALND is associated with several side effects including arm edema, numbness, pain and affected arm mobility. Hence, avoiding ALND may substantially improve a patient's quality of life. SLNB was first employed in the treatment of parotid tumors and melanoma [9-10], and breast cancer seemed to be another good model for this procedure. Indeed, SLNB in breast cancer was found to accurately predict the status of the entire axilla [11]. Armando Giuliano (USA) used blue dye, while Veronesi (Italy) used radiocolloid to identify SLN in breast cancer and both successfully demonstrated axillary nodal involvement [9-10] and the combination thereof was more reliable than either used alone [11-12]. A series of randomized studies confirmed a similar OS with SLNB and lymphadenectomy in breast cancer patients with clinically negative axillary lymph nodes [13-16]. In consequence, patients with a negative SLNB are currently managed without ALND. Further studies showed that even patients with 1-2 positive SLNs may forego ALND without compromising OS, provided surgery is followed by post-operative radiotherapy including the axilla [17-18]. ALND may also be avoided in node positive patients who achieve negative SLNB following pre-operative chemotherapy [19].

The rise of peri-operative systemic therapies

While Halstead was right on certain points, his theory did not consider breast cancer as a systemic disease. Understanding that breast cancer deaths are caused mainly by the tumor dissemination led to studies of adjuvant systemic therapies.

The first major study investigating adjuvant chemotherapy after surgery in breast cancer was published by Bernard Fisher et al in 1968 [20]. The authors concluded that single cytotoxic agent thio-tepa administered postoperatively in pre-menopausal patients decreases the risk of cancer recurrence death. In 1976, the Italian oncologist Gianni Bonadonna presented a spectacular benefit of postoperative multi-drug regimen including cyclophosphamide, methotrexate and fluorouracil (CMF), which later became the standard adjuvant treatment in breast cancer [21]. These findings were supported by other large trials performed by the NSABP and other research teams [22-25]. In the 1980s, chemotherapy improved from CMF to regimens including anthracyclines (doxorubicin, epirubicin), followed by the even more effective taxane combinations (paclitaxel, docetaxel) [26-30] in the 1990s [29-33]. With increasing evidence supporting survival benefit of adjuvant chemotherapy, in 2001 the NIH recommended its use in the majority of women with localized breast cancer, regardless of lymph node, menopausal or hormone receptor status [31].

More recently, there is an increasing trend of administering chemotherapy in the pre-operative period, rather than post-operative [32]. This approach aims at eradicating potential occult micrometastases present already at diagnosis and reducing tumor mass to enable curative mastectomy or even BCS in selected cases. Pre-operative chemotherapy results in remission of nodal metastases, thus allowing for less extensive axillary surgery and for tailoring postoperative radiotherapy [36]. Additionally, administration of chemotherapy prior to surgery provides vital information on tumor behavior *in vivo*, allows chemosensitivity assessment and offers pathological complete response (pCR) as a surrogate outcome marker of clinical benefit [3, 33]. Currently, pre-operative chemotherapy is routinely used in locally advanced and large primary breast cancers and provides apparent benefit in more aggressive phenotypes, such as triple negative and HER2-positive breast cancer. There was a word of warning regarding this strategy, however. Namely, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed no difference between pre- and post-operative chemotherapy in terms of all-cause mortality, but there were more local recurrences (21.4% vs. 15.9%) with the former, likely due to more BCSs in this setting [34]. These data indicate the need to mitigate the risk of local failure in patients managed with induction chemotherapy.

Targeted therapies

The starting point of targeted treatment of breast cancer was anti-estrogen receptor (ER) therapy. In 1977, the US Food and Drug Administration (FDA) approved tamoxifen as the first clinically viable selective ER modulator for metastatic breast cancer. Anti-estrogen therapy was a noteworthy breakthrough, because it had a greater global impact than any other therapeutic intervention in oncology.

Several large studies demonstrated that tamoxifen in ER-positive breast cancer significantly improved the post-operative outcome. Another EBCTCG meta-analysis demonstrated a 9.2% improvement of 15-year overall survival (OS) after a 5-year therapy of tamoxifen in ER-positive or ER-unknown breast cancer [35]. Tamoxifen

began to gain a proven position in cancer prevention, treatment of ductal carcinoma *in situ* (DCIS) and in early and advanced invasive breast cancer. Subsequently, a series of large clinical studies demonstrated higher efficacy of aromatase inhibitors (anastrozole, letrozole and exemestane) in hormone-sensitive breast cancers [36]. Extending hormone therapy beyond the standard five years allowed for an increase of DFS in patients with a higher risk of relapse [37-38]. Another approach for increasing DFS was combining tamoxifen or an aromatase inhibitor with a pharmacologic ovarian suppressor in high risk premenopausal women [39]. A recent development in the treatment of ER-positive advanced breast cancer was combining adding cyclin-dependent kinase 4 and 6 inhibitors (palbociclib, ribociclib and abemaciclib) [40-42]. These compounds act at the G1-to-S cell cycle checkpoint, leading to cell cycle arrest [43]. Advances in molecular biology, identified PIK3CA/mTOR signaling as a mechanism of resistance in ER-positive tumors, and the PI3K inhibitor alpelisib has shown promising activity [44].

Another milestone in the development of patient-tailored therapy was the discovery of the *HER2-neu* protooncogene in the 1980s [45-46]. Amplification or overexpression of this gene played a key role in the development and progression of an aggressive form of breast cancer called HER2-positive cancer. This discovery initiated the era of anti-HER2 therapy. The first anti-HER2 drug approved by the FDA was trastuzumab (Herceptin), a humanized monoclonal antibody. Clinical benefit of trastuzumab added to chemotherapy in HER-2-positive advanced breast cancer was first demonstrated in 2001 by Slamon et al [47]. Subsequently, a series of large randomized studies showed a spectacular efficacy of this compound in the adjuvant setting in patients with an overexpression or amplification of HER2 [48].

Within the next 20 years the array of anti-HER2 therapies has expanded to include small molecule tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib), second-generation monoclonal antibody pertuzumab and conjugates of trastuzumab with cytotoxic agents (trastuzumab emtansine, trastuzumab deruxtecan).

Breast cancer as a heterogeneous disease

Currently it is understood that breast cancer is a clinically and pathologically heterogeneous group of pathologic entities with different biologic and clinical behaviors. Immunohistochemistry techniques allow for the distinction of hormone receptor (ER or progesterone receptor, PR)-positive, triple-negative and HER2-positive breast cancers. In the 21st century genetic profiling led to the classification of breast cancer into five intrinsic molecular types: luminal A, luminal B, HER2-enriched, basal-like and normal-like breast cancer [49].

These subtypes are characterized by different clinical behavior and their distinction provides relevant information beyond pathology-based classifications [50]. In daily clinical practice, intrinsic molecular subtypes are replaced by their surrogates based on the immunohistochemistry expression of hormone receptors, overexpression of HER2, and a Ki67 score which is a cellular marker of proliferation. This classification is routinely used in clinical practice to assess prognosis and to select adjuvant systemic therapies in breast cancer patients (Table 1).

Table 1. Principles of perioperative systemic therapy for breast cancer

Phenotype		Subtype	Endocrine therapy	Anti-HER2 therapy	Chemotherapy
Hormone receptors	HER2				
+	−	Luminal A or luminal B HER2-negative	Yes	No	Yes (if high risk)
+	+	Luminal B HER2-positive	Yes	Yes	Yes
−	−	Triple negative	No	No	Yes
−	+	HER2-positive	No	Yes	Yes

Can molecular signatures predict prognosis?

The use of perioperative chemotherapy resulted in declining breast cancer mortality rates on a global scale. Moreover, the effectiveness of chemotherapy allowed for more conservative breast and axillary surgery. There was however a general conviction that adjuvant chemotherapy may be avoided in a proportion of patients, however there were no reliable instruments to predict individual risk of relapse.

Better understanding of molecular biology led to the development of several multigene tests which better predict prognosis of breast cancer and select patients to chemotherapy. Some examples of these assays include Oncotype DX® (Exact Sciences, United States), MammaPrint® (Agendia, Netherlands), Endopredict (Sividon Diagnostics GmbH, Koln, Germany), PAM50/Prosigna (Nanostring Technologies, USA) and Breast Cancer Index SM (bioTheranostics, USA) [51]. Two of these assays have been subjected to large randomized trials: MINDACT and TAILORx. The first trial, using MammaPrint test (a 70-gene signature), demonstrated that chemotherapy may be avoided in both low genomic (according to the signature) and low clinical (small tumor, N0, low grading) risk groups [52]. Whereas the second trial (TAILORx) using Oncotype DX (a 21-gene signature) showed no benefit from adjuvant chemotherapy for node-negative ER-positive and HER2-negative breast cancer patients with an intermediate recurrence score [53]. Importantly, this subset constituted around 70% of patients in the study group and with a standard clinical criteria most of them would be exposed to unnecessary chemotherapy. Whereas first-generation signatures (MammaPrint, OncotypeDX, Genomic Grade Index) reliably predict a five year prognosis, newer assays (Breast Cancer Index, EndoPredict, PAM50) are also prognostic for late recurrence, enabling patient survival to be prolonged by adjuvant endocrine therapy [54].

Unfortunately, multigene signatures have several limitations. First, their prognostic utility is restricted to ER-positive, T1-2 breast cancers with 0 to 3 positive lymph nodes. Since these test use ER-related and proliferation genes, they assign all ER-negative tumors to a high-risk category [58]. There is also a 20-30% discordance between particular multigene signatures in predicting the risk for individual patients [54, 56-58]. Finally, molecular assays do not indicate the most effective chemotherapy regimen and do not allow for the development of new strategies in high risk groups. Despite these shortcomings, prognostic signatures provide useful information and have been adopted by the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and the St. Gallen guidelines as a useful tool in helping physicians to make decisions about adjuvant treatment in ER-positive breast cancer patients [54, 59-62].

Improving the breast cancer survivors' quality of life

Significant progress in breast cancer treatment has resulted in increasing the number of survivors facing treatment-related side effects. Chemotherapy used for breast cancer often induces early menopause, may be cardiotoxic, ototoxic, neurotoxic and even carcinogenic. Endocrine treatment increases the risk of endometrial cancer, thromboembolic events, cataracts, osteoporosis, bone fractures, metabolic disorders (aromatase inhibitors) and hot flashes (tamoxifen). The anti-HER2 antibody (trastuzumab) is cardiotoxic and causes infusion-related reactions. Surgical treatment, particularly mastectomy, is disfiguring and affects both physical and psychological health. Finally, radiotherapy of left-sided tumors may induce late cardiotoxicity. Apart from the increasing treatment efficacy, an important aim of current approaches is therefore maintaining a good quality of life during and after treatment. Examples of these developments include breast reconstruction, effective antiemetic treatment, caring for bone health, and prevention of alopecia and neuropathy. Cancer support groups are proven to be effective for patients, spouses and other family members in reducing the emotional burden of a cancer diagnosis and treatment [63]. Another valuable aspect of supportive care in breast cancer patients is reducing the risk of treatment-related infertility [64].

Physical and mental rehabilitation after cancer treatment is not only vital for patients and their families but, given a high incidence of this malignancy, also has an important economic value. The prevalence of the return to work rate (RTW) is in the range of 43% to 93% within one year of diagnosis [65]. As a large majority of women with breast cancer are still in their working age, a low RTW may put considerable burden on a national economy [66].

Current challenges and outlook for the future

Fundamental changes in breast cancer management, as well as the implementation of large-scale mammography screening programs resulted in remarkable progress in therapeutic outcomes. For example,

between 1975 and 2002, the 10-year survival in the USA increased from 65% to 83% [67]. In consequence, the mortality from breast cancer in the USA decreased by 34% from 1975 to 2010, despite an incidence increase by 30% [67]. However, several major challenges remain for the current and next generation of physicians and scientists [68]. There are still no effective primary prevention measures. Tamoxifen, raloxifene and aromatase inhibitors (exemestane, anastrozole) have proved to decrease breast cancer risk [69-72]. However, they prevent only ER-positive breast cancers, do not provide survival benefit and carry considerable toxicity with long-term administration. Lifestyle changes to prevent breast cancer are not feasible for many women and their impact on survival can be modest.

Mammography has a proven role in screening for breast cancer, but it may also result in overdiagnosis and overtreatment of screened populations [73]. Therefore, there is a need for new tools to customize this method considering its benefits and perceived harms.

Systemic therapies sometimes fail to target micrometastases in the adjuvant setting and resistance to these drugs is a problem. An excellent diagnostic tool is a “liquid biopsy” exploiting circulating tumor cells or circulating tumor DNA or microRNA from a patient's blood. It can address monitoring of minimal residual disease after treatment, or even inform the selection of the most effective therapies [74-76].

Targeted biologic therapy has significantly transformed oncology, however triple-negative breast cancer seems to lack any target and there has been little progress in this worst prognosis entity [50]. Anti-HER2 therapies have upgraded the outcomes of HER2-positive breast cancer to the level of less aggressive subtypes, but the standard monoclonal antibody treatment does not combat occult brain disease which is particularly common in this subset. Recently, this shortcoming has partly been overcome though, with small molecule HER2 tyrosine kinase inhibitors [77].
Breast cancer treatment is moving towards a more individualized approach. Figure 1 outlines five major factors influencing the selection of systemic therapies for breast cancer patients. Better prediction of tumor response has led to the evolution of adjuvant systemic therapies from being based on the level-of-risk to considering first the expected response to treatment (Figure 2). Future endeavors hope to further develop tailored treatment based on patient pharmacogenomics and tumor molecular features. One approach that holds promise in the field of personalized therapy are immune and microenvironment gene signatures which, as opposed to current multigene assays, can predict prognosis also in ER-negative tumors [78-79].

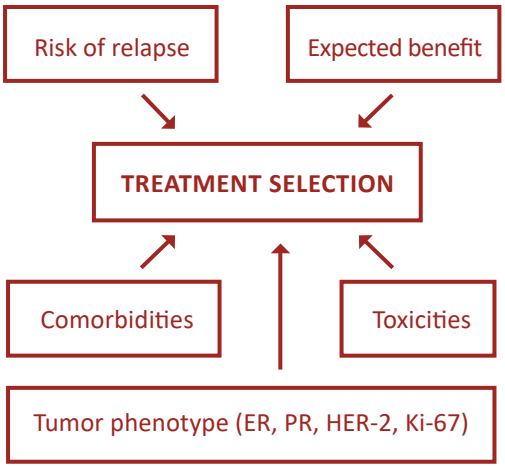

Figure 1. Major factors influencing the selection of systemic therapies for primary breast cancer
Abbreviations: ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2

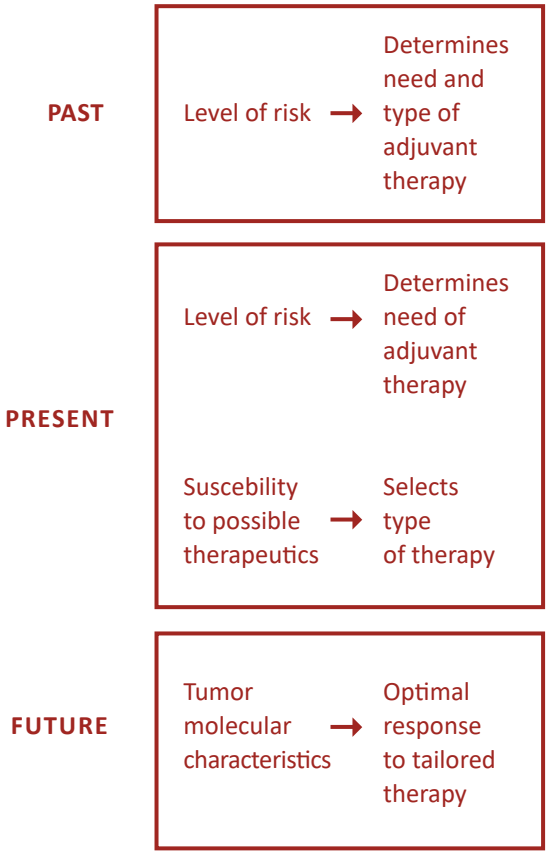

Figure 2. Conceptual evolution in selecting adjuvant systemic therapies

Conclusions

The paradigms in the treatment of breast cancer have changed considerably over the past century. Today, a more conservative surgery improves a breast cancer patients' quality of life without compromising survival and the axillary lymph nodes may be saved in a majority of patients. Adjuvant systemic therapies have reduced mortality and transformed breast cancer from a terminal illness into a curable one. Molecular biology has elucidated disease mechanisms and led to the development of truly personalized medicine. Despite these advances, there are still several challenges. Future research should be focused on developing valuable preventive strategies, better screening tests and images, better predictive gene assays and more effective therapies for the worst outcome subtypes.

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REVIEW ARTICLE

Vascular complications in patients with Autosomal Dominant Polycystic Kidney Disease. A review of the literature and current clinical recommendations

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Abstract

Autosomal dominant polycystic kidney disease is the most common genetic cause of renal failure. Apart from kidney involvement, patients are at risk of extra-renal manifestations, including vascular lesions. The etiology of vascular changes is diverse and depends, among other factors, on polycystin gene mutation, increased activity of the renin-angiotensin-aldosterone system and the occurrence of hypertension. The observed vascular system complications include cerebral artery aneurysms, cervico-encephalic arteries' dissection, aortic aneurysm and dissection and intracranial arterial dolichoectasia. This article discusses the etiopathogenesis, symptomatology, principles of prevention and treatment of the aforementioned diseases of the vascular system accompanying polycystic kidney disease.

Keywords: aneurysm · kidney · cyst · polycystin

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of renal failure. Its incidence in the general population is estimated at 1/400-1/1000 people. ADPKD is a disease inherited in an autosomal dominant manner with an estimated 50% risk of transmission to offspring. It is estimated that approximately 10% of all patients requiring kidney replacement therapy are suffering from this disease. ADPKD is a systemic disorder which results in cystic changes in the kidneys, liver, pancreas, seminal vesicles, ovaries and central nervous system (CNS), as well as non-cystic complications such as inguinal hernia or diverticulitis. Among people with genetic mutations that cause ADPKD, changes in the cardiovascular system are also more frequently observed [1-2].

Material and methods

This is a narrative type of review. We conducted a search of Medline-Ovid database (1990 to December 2019) using a key: *polycystic kidney disease* and its abbreviations (e.g. PKD, ADPKD) combined with a term *vascular.* In the next step, we excluded all articles that did not reference ADPKD. The relevance and eligibility of the retrieved records were considered by two authors, independently.

Pathogenesis of vascular changes in ADPKD

Mutations in the genes encoding polycystin 1 (*PKD1*) and polycystin 2 (*PKD2*) are present in ADPKD. In individual cases, the disease may arise as a result of mutations also in other genes (e.g. *GANAB* and *DNAJB11*) [3]. The *PKD-1* mutation occurs in about 85-90%, and *PKD-2* in about 10-15% of people with a clinical manifestation of ADPKD. Both genes code for membrane proteins that are among the building blocks of fast calcium channels, responsible for intracellular transport. Disfunction of this channel leads to increase in cAMP and promotes cell proliferation. Synthesis of cAMP is also stimulated by vasopressin, whose concentration is higher in ADPKD patients compared to the general population [1-2, 4]. Both polycystin 1 and polycystin 2 are found in smooth muscle and vascular endothelium, therefore mutations in genes coding these proteins are responsible for damage to the vascular wall [5].

In ADPKD, endothelium damage occurs in the early stages of the disease. This is due to the reduced activity of nitric oxide synthase in the vascular endothelium, which results in impaired vasodilatation. Another vasoconstrictive factor in patients with ADPKD, is the elevated level of endothelin I. Endothelin I is produced by the epithelium of the renal cyst and secreted into its lumen [6-7]. In this way, the balance between vasodilatation and vasoconstriction is disturbed. In addition, renal cysts press on renal vessels which leads to ischemia of renal parenchyma and activation of the renin-angiotensin-aldosterone (RAA) system.

In the early stage of the disease, RAA stimulation leads to hypertension, which directly damages vascular system, and is the main symptom of ADPKD [6]. Hypertension is observed in 60% of adults with ADPKD with normal renal function [7]. The average age upon diagnosis of hypertension in these patients is 32 years for men and 34 years for women [8]. In addition, hypertension affects approximately 20-30% of children with ADPKD [6].

Atherosclerosis is more common in the course of ADPKD. Thickening of the inner and middle layer of the vessel allows to determine the degree of atherosclerosis. The intima media thickness (IMT) is a predictor of the development of cardiovascular diseases as well as an early marker of vascular complications. It was proposed that the IMT is greater in young patients and that the thickening of IMT occurs early in asymptomatic patients [9-10]. IMT is examined by Doppler ultrasound of the cervical arteries by measuring the thickness of the middle and inner membrane layers, 1 cm proximal to the division of the common carotid artery. In ADPKD patients with normal blood pressure and with normal kidney function, the IMT value is significantly higher than in the general population. This is crucial because cardiovascular diseases are the leading cause of death among ADPKD patients [9].

Intracranial aneurysms

Due to significant risk of death and disability in the course of CNS bleeding, intracranial aneurysms (also called cerebral or brain aneurysms) are the most dangerous of all the extra-renal manifestations of ADPKD [11]. They occur in about 6% of patients with ADPKD without any family history of intracranial aneurysms and as many as 16% of patients with such family history [12]. In the general population, the incidence of intracranial aneurysms is estimated at 1-2% [13] (Table 1). Their occurrence is slightly more common in women, the incidence increases with age, and the peak of their occurrence, according to different authors, falls on the fourth or sixth decade of life [14-16]. There are two types of intracranial aneurysms (85% are saccular and 15% are fusiform) and they form as a result of damage to the elastic central membrane

Table 1. The incidence of vascular complications in patients with ADPKD

	ADPKD	General population
Intracranial aneurysm	6-16%	1-2%
Cervical artery dissection	unknown	Circa 3/100 000/year
Intracranial arterial dolichoectasia	2%	0.06%
Coronary artery aneurysm	unknown	In 0.15-5.3% of coronary angiographies performed
Aortic aneurysm	5-10%	2-4%

Abbreviations: ADPKD – autosomal dominant polycystic kidney disease

of the vessel [17]. 90% of the aneurysms are located in the anterior circulation of the brain, most often in the internal carotid, middle cerebral and anterior communicating arteries). Posterior circulation aneurysms are much less frequent. Most of the aneurysms have a diameter < 6mm, with an average of 3.5 mm (3 mm for women and 4 mm for men) [16-18].

In most cases, intracranial aneurysms grow asymptomatically. Some of the aneurysms cause a local mass effect, sometimes the cerebral ischemia is caused by clot material released from the dome of the aneurysm. However, an aneurysm rupture and SAH (subarachnoid hemorrhage) is observed in only about 0.3-2.3% of the cases [16].

The risk of aneurysm rupture increases with its diameter. Depending on their location, aneurysms located in the posterior circulation rupture more often. In the case of anterior circulation, the risk of hemorrhage increases when the diameter of the aneurysm is > 7 mm. In the posterior cerebral circulation, it is independent of the diameter [19]. Additional independent risk factors for aneurysm rapture and SAH are alcohol abuse, nicotinism and poor blood pressure control [20].

The main symptom of aneurysm rupture is sudden and severe headache (often referred to as "the most intense headache of my life"). It is also worth to remember about the so-called warning pains that often occur few weeks earlier. About half of the patients lose consciousness. Epileptic seizures appear in approximately 10% of patients with subarachnoid hemorrhage. Meningeal signs are not specific for SAH. We observe neurological symptoms depending on location and extent of the haemorrhage [17]. The diagnostic method of choice in cerebral hemorrhage is non-contrast computed tomography (CT). In the absence of blood in CT scans, a lumbar puncture should be performed to confirm the presence of erythrocytes or haemolysis products (bilirubin, oxyhemoglobin) in the cerebrospinal fluid [17].

There are two available methods for the treatment of aneurysms: neurosurgical clipping and endovascular. The first method requires craniotomy, therefore it carries a surgery-related risk for the patient, e.g. clip slippage due to incomplete clipping and insufficient amount of used clips [17]. Vascular clips are placed on aneurysms which are not appropriate for endovascular treatment, e.g. large aneurysms and those with a wide neck. The endovascular method is based on embolization of the aneurysm (by means of so-called *coils*) and excluding it from the cerebral circulation. This treatment is less risky and reduces the danger of patient's disability. In case of SAH, endovascular embolization should be performed up to 3 days from the onset of symptoms [12, 17].

Preventive treatment consists of excluding aneurysms with potential for rupture from the circulation and has significant challenges. On the one hand, this procedure has the potential to significantly reduce the mortality of patients with cerebral artery aneurysm and ADPKD. On the other hand, it is necessary to take into account the increased surgery risk, frequent detection of small aneurysms (with low risk of rupture) in brain imaging. In addition, at the moment there is a lack of reliable radiological, biochemical or genetic markers that would help assess the risk of aneurysm rupture in an ADPKD patient, thus justifying a preventive procedure [22].

The most common complication of bleeding from a ruptured aneurysm is re-bleeding and secondary CNS ischemia. About half the of patients with SAH die and 10-20% of those who survive remain severely disabled. There is also an increased incidence of another rupture in the cerebral artery aneurysm in patients who have had such an episode in the past [17].

Monitoring of intracranial aneurysms in patients with ADPKD

The method of choice in the imaging of intracerebral aneurysms is magnetic resonance angiogram (MRA). This method does not require use of any contrast agents, thus eliminating the risk of nephrotoxicity (as opposed to angio-CT) or systemic complications (as in the case of gadolinium-based contrast in MR) in patients with impaired renal function. Its limitations are contraindications to perform MR, such as the presence of metal implants, vascular clips or lack of patient's cooperation with the procedure [23].

The indication for screening via MRA of the brain is the presence of symptoms suggesting an aneurysm or family history of cerebral aneurysm or intracranial hemorrhage. This imaging should also be performed in the group of ADPKD patients performing high-risk occupations, e.g. pilots, drivers [15]. In this group of patients, the screen should be repeated every 5 years. In patients with a family history of aneurysms, MRA should be performed every 5-10 years [13, 24-26]. Recent literature suggests the benefits of conducting screening tests also in patients without any family history, i.e. in cigarette smokers, in patients before starting oral anticoagulants, in patients qualified for renal transplantation or surgery requiring long-term oral anticoagulants and in those who are very concerned about the risk of brain aneurysm [27] (see Table 2).

Cervico-encephalic artery dissection

Cervico-encephalic artery dissection is a relatively rare complication of ADPKD. Its incidence in the general population is estimated at 3/1000 people, however specific data about incidence in the ADPKD population is not available [16]. The most frequently affected vessels are the internal carotid artery (~75% of cases) and vertebral artery (~15%). We distinguish two types of dissection: spontaneous and post-traumatic. The etiological factors causing artery dissection in ADPKD include arterial hypertension and defects in the vessel wall structure. Dissection occurs as a result of damage to the inner membrane, its separation and the passage of blood between the inner and middle membrane of the vessel, thus creating the so-called false lumen. Post-traumatic dissection usually occurs in younger patients (about 30 years of age), in contrast to spontaneous dissection whose peak is observed about 50 years of age.

The main symptom of internal carotid artery dissection is a severe headache, most often in the frontotemporal area. The pain is usually develops gradually, is not sudden and is accompanied by symptoms of focal neurological signs and Horner syndrome. In the case of dissection of the vertebral artery, the pain appears in the occipital region, in addition to neurological signs from the vertebrobasilar circulation.

Doppler ultrasound examination is the method of choice in case of suspected cervico-encephalic dissection, which should be confirmed with MR (FAT-SAT sequence) with cerebral arteries assessment. Treatment consists of taking oral anticoagulants for 3-6 months [28-30].

Intracranial arterial dolichoectasia

Dolichoectasia is the elongation and widening of the vessels. Specifically, the damage occurs to the inner and middle membrane of the vessel. In the brain, dolichoectasia usually occurs in the vertebral arteries and the basilar artery. This pathology occurs in approximately 2% of patients with ADPKD, compared to 0.06% in the general population [30]. Most patients with dolichoectasia are asymptomatic and this change is detected accidentally. Rarely, patients suffer ischemic stroke in the course of basal/vertebral artery clot or embolism caused by thrombotic material. Occasionally, cranial nerves are damaged, increased intracranial pressure and hydrocephalus take place. Surgical treatment is not recommended in the case of intracranial artery dolichoectasia [31].

Aneurysms of coronary arteries

In addition to classic ADPKD complications in the myocardium, such as hypertrophy or valve defects (the most common is mitral valve prolapse), cases of coronary aneurysms are described [32]. The criterion for the diagnosis of coronary aneurysm is > 1.5-fold widening of the vascular lumen in relation to the diameter of the widest coronary vessel in the patient. Right coronary artery and anterior descending artery aneurysms are the most common, whereas circumflex artery and left coronary artery aneurysms are less frequent. Coronary aneurysms may be asymptomatic. However, angina pain often occurs due to myocardial ischemia secondary to embolic material released from the aneurysm lumen. The complication may also be acute coronary syndrome and arrhythmias. Very rarely, the ruptured aneurysm may cause pericardial tamponade. Small aneurysms do not usually require invasive treatment such as endovascular stent implantation and cardiac surgery (in the case of multiple aneurysms or those of very large sizes) [33].

Aortic aneurysm

Aortic aneurysms in patients with ADPKD are most often found in the abdominal part, mainly in patients with advanced renal failure requiring dialysis. The

Table 2. An overview of the recommendations for monitoring intracranial aneurysms in patients with ADPKD

	PTN-working group [11]	KHA-CARI [39]	Spanish Working Group on Inherited Kidney Diseases [40]	KDIGO [24]
Year published	2019	2015	2014	2015
Imaging method	MRA	• MRA with contrast if eGFR > 30ml/min/1,73m, • non- contrast MRA if eGFR < 30ml/min/1,73m^2 or CT angiography in patients with normal kidney function	MRA	MRA
Screening recommendations	**1.** In people with a positive family history of cerebral aneurysm, SAH or sudden death of a family member with ADPKD. **2.** can be considered in: – people in high-risk occupations (e.g. pilots), – patients qualified for renal transplantation or other procedure requiring general anasthesia, – cigarette smokers, – before starting oral anticoagulant therapy, – people who are concerned about ICA.	**1.** In people with a positive family history of SAH, intracranial bleeding and/or unruptured brain aneurysm in a family member in the first line of relationship. **2.** can be considered in: – people who perform high risk occupations, – cigarette smokers, – in patients with uncontrolled AH, – in patients qualified for renal replacement or surgery that require long-term oral anticoagulants, e.g. heart valve replacement, – before starting oral anticoagulant therapy.	**1.** In people with a positive family history of cerebral aneurysm or stroke. **2.** In patients with symptoms of brain aneurysm. **3.** In patients who train a sport or have a hobby where loss of consciousness is life-threatening. **4.** In patients who are eligible for renal replacement or surgery that require long-term oral anticoagulants (e.g. heart valve replacement). **5.** In people who are very concerned about the risk of ICA.	**1.** In people with a positive family history of cerebral aneurysm, SAH. **2.** In with history of aneurysm rupture. **3.** In patients in high-risk occupations. **4.** In patients who are concerned about the risk of ICA.
Re-screening	Every 5 years	Every 5-10 years	Every 10 years	Every 5-10 years

Abbreviations: AH – arterial hypertension; ADPKD – autosomal dominant polycystic kidney disease; CT – computed tomography; eGFR – estimated glomerular filtration rate; ICA – intracranial aneurysm; KDIGO – Kidney Disease: Improving Global Outcome; KHA-CARI – Kidney Health Australia – Caring for Australasians with Renal Impairment; MRA – magnetic resonance angiography; PTN – Polskie Towarzystwo Nefrologiczne (Polish Society of Nephrology); SAH – subarachnoid hemorrhage

incidence is estimated at approximately 5-10% of patients, compared to 2-4% in the general population. It is controversial whether or not the formation of aortic aneurysms is directly related to kidney disease or results from hypertension and atherosclerotic lesions that are common in patients with ADPKD. Currently there are no indications to screen for aortic aneurysms in patients with ADPKD differently than in the general population [13]. In Poland, as a part of the *National Screening Program for Abdominal Aorta aneurysm in 2018-2020*, people over 65 years of age who have at least 3 of the risk factors (e.g. hypertension, male gender, hyperlipidemia, coronary disease and tobacco smoking) are eligible for screening. Similar screening programs are offered in other countries, e.g. the United Kingdom. The possibility of aortic dissection or rupture of the abdominal aortic aneurysm should be considered in every patient with ADPKD, who experienced sudden severe abdominal pain of unknown origin. For technical reasons, visualising abdominal aorta aneurysms using ultrasound may be hindered by the enlarged polycystic kidneys.

Thoracic aortic dissections are relatively rare in patients with ADPKD, while they are characteristic of patients with Marfan syndrome. Two types of dissection are distinguished according to the Stanford classification: type A (the dissection includes the ascending aorta with or without the descending part) and type B (dissection occurs only in the descending aorta). Type A dissection is noted in about 60-70% of patients, whereas the rest have type B dissection. In type A dissection the mortality is about 50% and these patients require surgical treatment. Severe chest pain radiating to the back in all patients is a life-threatening condition and may mean dissection of the aortic thoracic segment [34-36].

Future perspectives

An increasing number of studies provide recommendations for monitoring aneurysm in ADPKD, however there are some points not clearly defined, such as the patient's age at screening, the frequency and duration of repeat screening, the use of follow-up imaging after intracranial aneurysm diagnosis. Recent literature suggests that screening for intracranial aneurysms with MR angiography in all patients with autosomal dominant polycystic kidney disease is cost-effective [37]. The high prevelance of aortic aneurysm is estimated in patients with ADPKD. Larger studies are needed to confirm the utility of specific echocardiographic screening as currently there is no such recommendation [38].

Conclusions

Polycystic kidney disease inherited in an autosomal dominant way is a disorder with many organs involvement. In some patients, non-renal symptoms, including vascular changes, occur. Mutations in the polycystin 1 and 2 gene are considered the main cause of vasculopathy. In the course of vascular wall damage, brain aneurysms may occur, the rupture of which leads to intracranial hemorrhage and often significant neurological deficits. It is very important to monitor patients from so-called risk groups for intracranial aneurysms – this allows the detection and treatment of aneurysms before they rupture. Cervico-encephalic dissections, aortic aneurysm and dissection, and cerebral vascular dolichoectasia are more common in ADPKD than in the general population. It has been proven that atheromatic changes happen much faster in patients with ADPKD and increase the risk of cardiovascular diseases, which are the main cause of death in these patients. The proper prophylaxis and reduction of vascular risk factors through correct treatment of hypertension, lipid disorders, cessation of smoking and alcohol abuse, as well as, propagation of other pro-health behaviors are of key importance for slowing down disease progression and reducing mortality.

Conflict of interest: none declared

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REVIEW ARTICLE

Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines

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Abstract

Background: Incidence of morbid obesity is rising worldwide. Current clinical practice guidelines for the pre-transplant evaluation of end-stage kidney disease (ESKD) patients lack clear recommendations on morbid obesity. **Material and methods:** The aim of this review was to summarize the current guidelines on the role and treatment of obesity in kidney transplant recipients. Eight current national and international clinical practice guidelines were identified in a comprehensive literature search. **Results:** All guidelines underline early detection of obesity and obesity-related comorbidities in ESKD patients. Only two guidelines explored the role of weight-loss surgery, however due to the lack of sufficient evidence no formal recommendation of surgical procedure was given. **Conclusions:** Diagnosis and treatment of obesity remains underappreciated in the current guidelines, most of which do not include pharmacological and surgical interventions. High-quality evidence is warranted to assess the role of weight-loss including surgery in ESKD patients and to update the recommendations in future guidelines.

Keywords: obesity · end-stage kidney disease · bariatric surgery

Citation

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Introduction

The number of obese and morbidly obese end-stage kidney disease (ESKD) patients is rising. Due to the obesity epidemic, nearly 60% of all kidney transplant recipients are overweight or obese, with male predominance [1]. Kidney transplantation (KT) is the most effective method of ESKD treatment but it is still a debatable whether obese patients are suitable candidates for KT [2-6]. Clinical practice guidelines (CPGs) review current research and formulate recommendations based on available evidence and expert opinion. Clear guidance regarding obesity assessment and treatment options would be an essential part for the selection process of candidates for KT. The aim of this review is to assess the availability, quality, and consistency of recommendations for obesity evaluation and treatment before KT included in current national and international CPGs for kidney transplant candidates.

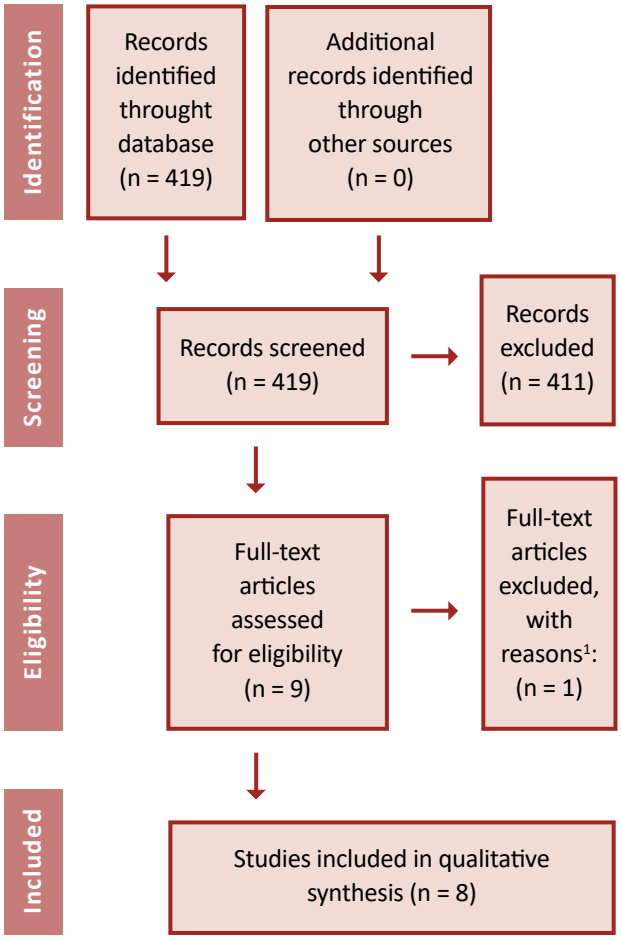

Figure 1. PRISMA flowchart.[1] Clinical Practice Guideline excluded due to lack of recommendation for inclusion to kidney transplantation [7].

Material and methods

A systematic review was performed according to Preferred Recording Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [7]. The search strategy included literature published until January 2020, using the following search query: ("kidney transplantation" OR ("kidney" AND "transplantation" OR "kidney transplantation" OR ("kidney" AND "transplant") OR "kidney transplant") AND ("Assessment") AND ("guideline" OR "guidelines"). Two researches independently searched and assessed the guidelines. We included only CPGs for the selection of candidates for deceased donor kidney transplantation. CPG for living donor kidney transplantation were excluded after screening due to identification of recommendation for obesity only in kidney donors [8-9]. The study protocol was presented in PRISMA flowchart (Figure 1). The following data were extracted: society, year of publication, inclusion of obesity into recommendation, recommendations for obesity treatment and grade of evidence.

Results

The literature search revealed 419 articles. A total of 411 were excluded during screening of titles and abstracts. The remaining 8 CPGs were searched for obesity evaluation recommendations. Key facts about the included studies are summarized in Table 1.

Recommendations for obesity evaluation before kidney transplantation

Three CPGs recommended that obesity should be routinely assessed at each pre-transplant consultation [10-12]. The included measurements should be as follows: patients height, weight, calculation of BMI. Additionally, waist circumference should be assessed when weight and physical appearance suggest obesity, but calculated BMI is < 35 kg/m^2 [10]. The definition of obesity in adults includes waist circumference ≥ 102 cm in men and ≥ 88 cm in women [11]. Two guidelines recommended weight reduction before transplantation if BMI exceeds 30 kg/m^2 [12-13]. One study set the upper limit of BMI to 40 kg/m^2 [14]. Another CGP states that in patients with BMI > 36 kg/m^2 the transplantation is associated with an unacceptably high risk of death and needs careful consideration [12]. All CPGs state that obesity of the kidney recipient byitself is not a contraindication for KT, however if co-existing with other comorbidities (e.g. advanced cardiovascular diseases, peripheral vascular

Table 1. Obesity in current clinical practice guidelines

Guidelines	Region	Obesity in candidates for transplantation	Recommendation in obesity
AST (2001)	USA	Obesity without comorbidities* is not a contraindication for KT (Level of evidence not provided).	Weight reduction (role of limited exercise in dialyzed patients) (Level of evidence not provided).
Canadian Society of Transplantation (2005)	Canada	Obesity without comorbidities is not a contraindication for KT (Grade C). In patients with BMI > 36 kg/m^2 KT is contraindicated.	• Weight reduction to BMI < 30 kg/m^2 • Surgical intervention for obesity may be considered in extreme cases (Grade B)
Bunnapradist & Danovich (2007)	USA	In patients with BMI > 40 kg/m^2 KT contraindicated.	Weight reduction (the benefit is unclear, method not specified) (Level of evidence not provided).
Lisbon Conference Report (2007)	Europe	In morbidly obese KT is contraindicated (BMI not applicable) (Level of evidence not provided).	No recommendation
KDIGO (2009)	Interna-tional	In patients with BMI > 30 kg/m^2 KT is contraindicated.	• Early diagnosis of obesity (Level of evidence not provided). • Obese individuals should be offered a weight-reduction programme (Level of evidence not provided). • Diet and other behavior modifications are safe in KT recipients (Level of evidence not provided. • Bariatric surgery may be performed safely in selected KT recipients (Level of evidence not provided).
KHA-CARI (2013)	Australia	No recommendation	• Obesity should be assessed at each visit (Grade C). • Diet and behavioral modification are likely to be safe. Diet that is individually planned with a moderate energy restriction of about 30% of energy expenditure, with monthly follow up with a dietician (Level of evidence not provided). • There is insufficient evidence to make recommendations or suggestions with respect to bariatric surgery (Level of evidence not provided).
European Renal Best Practice Guideline (2015)	Europe	BMI > 30 kg/m^2 is a contraindication for KT (Level of evidence not provided).	Obese patients should reduce weight before KT (Level of evidence not provided).

* advanced cardiovascular, peripheral vascular, liver or pulmonary disease, HIV, active hepatitis, active pulmonary or systemic tuberculosis

diseases, liver or pulmonary disease, active hepatitis) it increases the risk of perioperative complications and may impair graft and patient survival [12, 15].

Recommendations for diet and behavioral therapy

These therapies were considered safe in ESKD population but they were related only to a short-term weight reduction [10]. Only one study clearly stated that overweight kidney transplant recipients should have an individually-planned diet with a moderate energy restriction of about 30% of energy expenditure, with dietician follow-up [11]. It recommended also to create a caloric deficit of 500-1000 kcal/day along with increased physical activity [11].

Recommendations for pharmacological obesity therapies

The analyzed CPGs briefly discussed the role and the risk of novel pharmacological weight reduction therapies [10-11]. There were no trials examining the safety of those interventions in this specific population. Two medications (orlistat and sibutramine) were mentioned in recommendations [10-11]. Orlistat is related to decreased absorption of fat-soluble vitamins and may also interfere with the absorption of immunosuppressive medications and may be associated with higher risk in ESKD patients [10]. Sibutramine may increase blood pressure and heart rate and is not advised in patients with cardiovascular risk [10].

Recommendations for bariatric surgery

Little was mentioned about bariatric surgery in the current CPGs. Two of eight CPGs recommend weight-loss surgery before kidney transplantation [10-11]. However, the quality of existing evidence was insufficient to form recommendations about qualification, procedure type or procedure timing (i.e. before or after the KT).

Discussion

The prevalence of obesity among patients with ESKD continues to increase. Obesity was shown to be an independent risk factor not only of the ESKD development but also to accelerate the progression of that disease [5]. Kidney transplantation is considered as gold standard in ESKD treatment. Obesity is now limiting the access to KT by delaying the enrollment to transplant list and prolonging the waiting time compared to the nonobese candidates [16-17]. Additionally, obesity is associated with inferior short-term results of transplantation [3, 5].

Current CPGs are consistent regarding a strong need of early obesity assessment before enrollment to transplant waiting list. Most guidelines use BMI to assess obesity for waiting listing purposes [10, 13, 18]. BMI < 30kg/m^2 prior transplantation is recommended but in some studies BMI below 35kg/m^2 is considered a selection criterion [19-20]. The limitations of BMI as a metric of body fat must be appreciated. Anthropometric measures (waist circumference and waist-to-hip ratio (WHR)) are considered as an alternative to BMI in body composition assessment. These measures were shown to have a direct association with increased cardiovascular mortality in dialyzed ESKD patients as well as post-transplant mortality more precisely than BMI [21-22]. The existing guidelines are based on available original studies at the time of their publication. All current clinical practice guidelines were published before 2015. The role of diet and pharmacological treatment was poorly discussed but the level of evidence is sufficient to consider them safe for kidney transplant candidates [10-11]. The surgical treatment of obesity was not included in most CPGs due to limited evidence on safety and outcomes of bariatric procedures at the time of their publication. Only two CPGs mentioned possible implementation of bariatric surgery in that indication [11-12]. Since then several large studies were published giving new insights into the management of obese ESKD patients [23-25]. The results of these studies are presented below. It is likely that these data will be included in new editions of CPGs.

Based on the current knowledge, the use of pharmacological interventions for the treatment of obesity is limited in ESKD patients. First, orlistat use in patients with chronic disease is contraindicated because of its association with acute kidney injury and chronic kidney disease due to increased absorption of oxalate and the risk of nephrocalcinosis, inflammation and kidney fibrosis as a result [26-28]. Moreover, post-transplant drug interaction, particularly with cyclosporin, results in reducing their bioavailability and limits its use [29]. Secondly, sibutramine was withdrawn from the obesity treatment due to unacceptable increased cardiovascular risk [30]. A newer drug lorcaserin, is associated with potential kidney benefit, but limited to the lower risk of new-onset of albuminuria. Its use in ESKD patients is contraindicated due to worsening of chronic kidney disease stage [31-32]. Bupropion, likewise, should not be used in ESKD patients [32-33].

The role of physical activity was discussed in only one guideline [11]. Research has shown that pre-

-transplant aerobic exercise, long-term progressive resistance exercise, resistance training, and home-based exercise are tolerable in patients with ESKD [34-35]. Interestingly, the aerobic exercise is not related to weight reduction but has an positive impact on dialyzed patients' quality of life [36]. After transplantation, aerobic exercise, resistance training and individualized progressive exercise programs are effective in weight--loss programs [34].

Feasibility and safety of bariatric surgery is currently investigated and discussed. A recent study has shown an increasing number of patients with ESKD undergoing bariatric surgery as a bridge to KT [23]. Nevertheless, no consensus was reached regarding the management options for obese KT candidates. It was previously believed that bariatric surgery use in ESKD patients may be limited because of higher mortality risk. However the safety and significance of weight loss surgery in ESKD patients increased over the years [25, 37-39]. Two bariatric procedures were preferred [23, 40]. LSG (laparoscopic sleeve gastrectomy) and LRYGB (laparoscopic roux-en-y gastric bypass) appear to cause effective weight-loss before KT and improve surgical access during transplantation [41-42]. Uncertainties exist regarding optimal timing of bariatric surgery [38]. It has not been proven yet if the bariatric procedure should be performed before or after engraftment. Both approaches are related to low risk of graft failure and low mortality in long-term analysis when compared to the mortality rate of obese patients without ESKD [43]. Complication rates of LSG were similar between patients with and without ESKD [23, 44]. It should be noticed that LSG performed before transplantation is associated with significant changes of pharmacokinetics of tacrolimus and mycophenolate mofetil (increased maximal concentration and decreased clearance) in that group of patients [45]. Whereas malabsorptive procedures are related to hyperoxaluria and increased risk of nephrolithiasis [46].

Interestingly, an obesity paradox was described in dialyzed patients [47-48]. It is associated with better survival of obese patients who were transplanted than all patients who stay on transplant waiting list. Howver these results may be confounded by worse outcome of malnourished ESKD patients [47, 49-50]. Moreover, obesity reduces the likelihood of being enrolled to the waiting list, but not the transplantation once enrolled, especially among women [17].

Recent large metanalyses support higher risk of KT of obese patients and better survival in lower BMI patients [51-53]. It was proven that kidney recipients have an inferior survival when their BMI is > 40 kg/m^2 [19, 54]. Recent metanalysis (of 209,000 patients) revealed lower mortality, delayed graft function (DGF), acute rejection, infectious complication rate and better 1-, 2- and 3-year survival in kidney recipients with BMI < 30 kg/m^2 [52]. In another metanalysis (17 studies, 138081 patients) obesity was demonstrated not to be related with higher mortality risk but was associated with higher risk of graft loss and DGF [53]. A metanalysis of 9296 patients confirmed higher risk of DGF but not acute rejection and death risk [55]. The results of those analyses support the necessity of obesity treatment in ESKD patients. Several studies investigated the benefits and risk of bariatric surgery in that group of patients [24, 56-58]. Laparoscopic SG has replaced Roux-en-Y gastric bypass (RYGB) as the most common bariatric surgical procedure in patients with ESKD [23]. SG in ESKD patients is not related to higher risk of leaks, reoperations, or mortality in 1 year follow-up [59]. Our center morbidly obese ESKD patients have similar weight loss results after bariatric procedure than non-ESKD [42, 44]. Nine of twenty of them underwent kidney transplantation without any perioperative complications and with good kidney function in follow-up. Patients who underwent KT after SG have good 1-year and long term transplantation results in small group analysis [58]. Morbidly obese patients after LSG experienced lower rates of DGF and readmission related to graft insufficiency in 1 year follow-up [58]. The mortality rate of obese individuals with ESKD after SG is lower (1.8/100 patient-years compared to 7.3 in the control group) [60]. Moreover, in stage 3 CKD significant improvement of kidney function was observed [60]. The emerging evidence from those studies supports the low risk and safety of bariatric surgery in ESKD patient.

Conclusion

In conclusion, the obesity epidemic has major implications on kidney transplant candidates' evaluation. In existing CPGs there is a consensus regarding the need of obesity assessment in transplant candidates. However, most of the evaluated CPGs are inconclusive concerning the role of pharmacological and surgical interventions for the treatment of obesity. New large--scale studies seem to be the missing link that suggests clear recommendations for obese patients' management. It seems necessary to update the guidelines with results of recent studies on the new measures in the assessment of obesity and its treatment, with special attention to surgical treatment.

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BIORESOURCE PAPER

Datasets and future research suggestions concerning SARS-CoV-2

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Abstract

We gathered publicly available online data and prepared a database of epidemiology, demographics, economics, Bacille Calmette-Guérin vaccination and online search trend statistics relevant to the coronavirus disease 2019 (COVID-19). Moreover, we provide several suggestions on the use of this bioresource and reference other relevant datasets to promote research on COVID-19.

Keywords: BCG · COVID-1 · SARS-CoV-2 · datasets · data · epidemiology · Google trends

Citation

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Introduction

The first case of atypical pneumonia, which later was diagnosed as the Coronavirus disease 2019 (COVID-19), was reported to be on December 31st 2019 in China. At that time COVID-19 attracted relatively little public or scientific interest internationally [1]. However, by March of 2020 the situation evolved to COVID-19 pandemic and the novel SARS-CoV-2 virus became the subject of numerous research articles. It is noteworthy that several scientific journals stopped publishing articles not related to SARS-CoV-2. COVID-19 quickly prompted much scientific research and several scientific journals have called for articles concerning SARS-CoV-2. Several online databases regarding COVID-19 are available from well-known institutions such as the World Health Organisation (WHO), the European Centre for Disease Prevention (ECDC) and Johns Hopkins University (JHU). Several other COVID-19 datasets were made available regarding online conversations on Twitter, summaries of scholarly articles and epidemiology [2–5]. Our bioresource is novel, as it provides not only a concise dataset on epidemiology but also additional data about demographics, economics, tuberculosis (Bacille Calmette-Guérin, BCG) vaccination and online search trends. After proper statistical analysis, this data may be used to draw novel conclusions. We hope this dataset will be of use to researchers, particularly to those at the beginning of their career.

Data sources and initiatives

Repurposing of data for research is supported by the WHO and other medical organizations worldwide as this type of collaboration may lead to the discovery of new information concerning the COVID-19 threat. There are three major sources of daily-updated COVID-19 epidemiology (i.e. incidence and mortality) data: WHO, ECDC and JHU as seen on Table 1. Third-party aggregators, such as GitHub scrape data from the above repositories to make it simpler to view and analyse. In some cases, users may need to create an account for free to download the information.

Due to the limited capacity and accessibility of testing for SARS-CoV-2 in many countries worldwide, there may be a substantial difference between the confirmed number of COVID-19 cases and the total number of COVID-19 cases (See Table 1).

Dataset to repurpose

The data sources shown in Table 1 provide the information about the following variables: incidence,

Table 1. Main data sources comprising the national COVID-19 incidence, mortality, country and population size

Acronym	Organisation	Website	Raw Data or GitHub
WHO	World Health Organisation	https://covid19.who.int/table	Raw Data
ECDC	European Center for Disease Prevention	https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide	Raw Data
JHU	Johns Hopkins University	https://coronavirus.jhu.edu/map.html	Data could be scrubbed https://github.com/CSSEGISandData/COVID-19/tree/master/csse_covid_19_data
OWD	Our World in Data	https://ourworldindata.org/covid-testing	third-party data, downloadable spreadsheets, visualizations are licensed under Creative Commons Attribution 4.0 International (CC BY 4.0)

mortality, country and population size. We added several new variables to the shared database:

- gross domestic product (GDP) and GDP per capita,
- the number of days since the first reported case in the country,
- the number of days since January 1, 2020 (the first report of the novel coronavirus in Wuhan, China),
- the number of days since January 25th 2020 (the first reported case in Europe),
- cumulative incidence/mortality in Europe and worldwide,
- incidence/mortality per 1000 citizens of a country,
- case fatality rate (CFR, the proportion of deaths from COVID-19 among all diagnosed individuals) was calculated. CFR in Europe/worldwide/country, indicated European countries and the European Union,
- tuberculosis (BCG) vaccination policies and practices [6].

Free statistical analysis software includes: *R* and *Past* [7,8]. In particular, the Past software supports a broad range of statistics such as Monte Carlo simulation, cross-correlation, analysis and removal of serial correlations in time series, principal coordination analysis, spherical data and Kernel densities. Moreover, the statistics derived from Past's palaeontological science category may be applied in various clinical analyses [9]. *MedCalc* software (free 15-day trial) may also be useful [10]. The logarithmic increase of COVID-19 cases in the early phase of the pandemic may be analysed with geographical data. Whereas *Our World in Data* provides interesting and free to use/embed graphs [11].

Potential uses

We suggest several research questions to potentially explore in future studies:

- What is the influence of the COVID-19 pandemic on global mortality due to other illnesses? To what extent does the overall mortality due to COVID-19 differ from a country's baseline mortality level? The EuroMOMO website [12] may be useful for this analysis as it provides information on all causes of mortality in 24 European countries.
- When, where and what kind of public policies significantly reduced the spread of COVID-19 and/or ended the epidemic? The effectiveness of public polices worldwide may be correlated with the graph shown in Figure 1.
- Are the incidence and/or CFR in a particular country correlated with its population density, social distancing policies and its society's adherence to restrictions? The information collected by *Our World in Data* could help group countries and continents based on their CFR and incidence as seen on Figure 2.

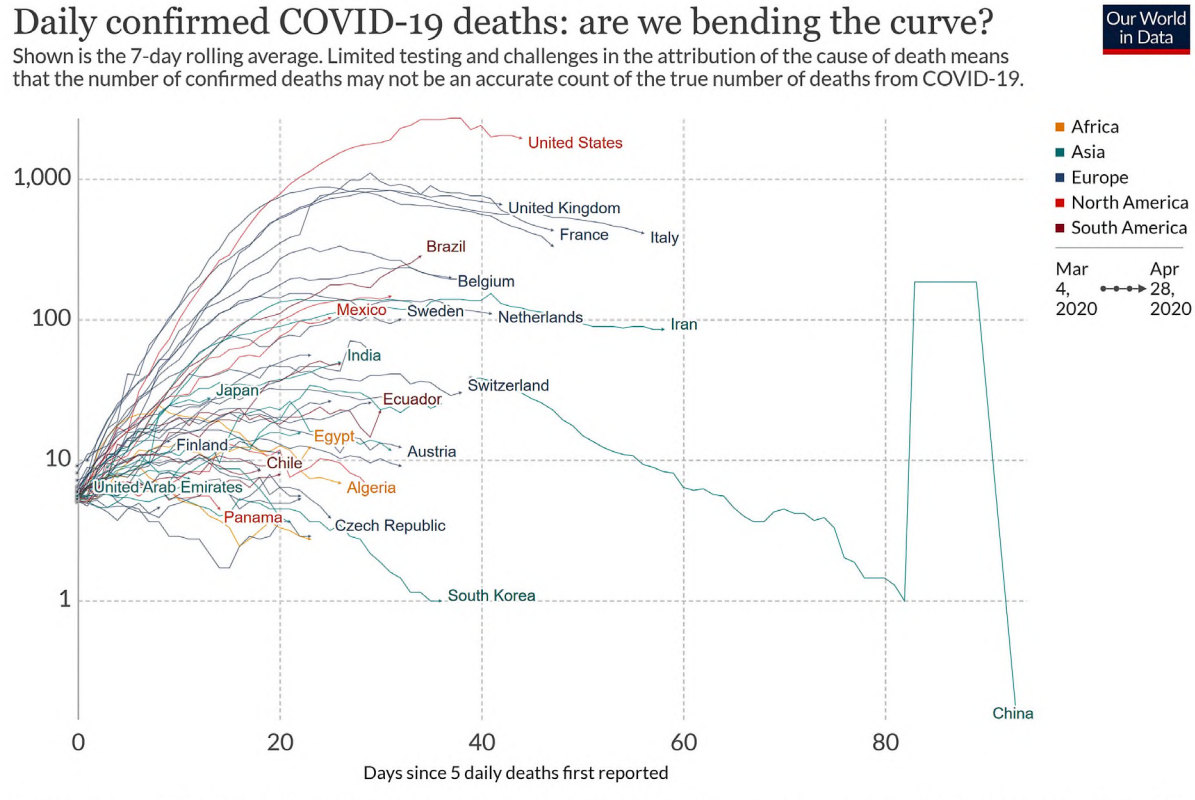

Figure 1. Daily confirmed COVID-19 deaths: are we bending the curve? [11]

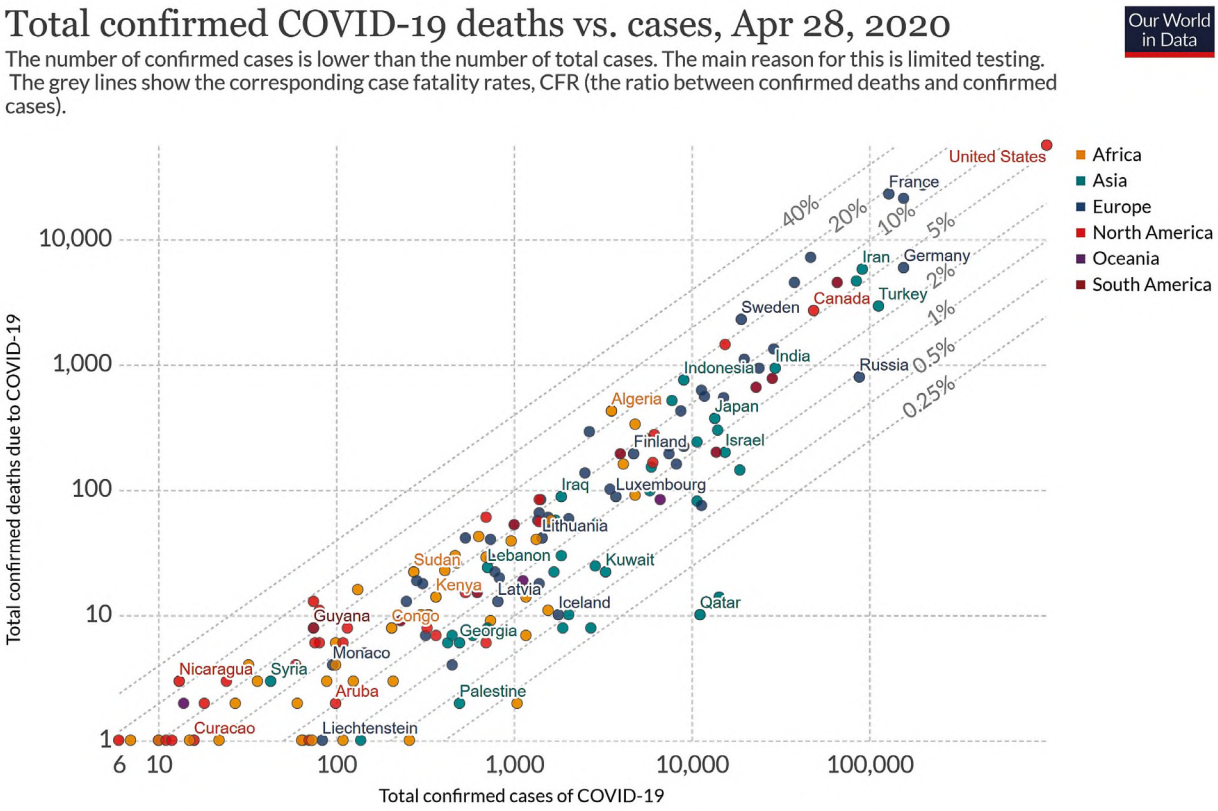

Figure 2. Total confirmed COVID-19 deaths vs. cases [11]

- Are the internet search trends correlated with the incidence and mortality of COVID-19 in a particular country? Or is this more due to media clamor? Google Trends may be helpful in this analysis [13].
- What is the educational quality of YouTube videos concerning COVID-19? Several studies were published on this topic [14–16]. The Google Chrome extension "vidIQ Vision for YouTube" may be used to access additional statistics that are normally not available on the YouTube website and provide the exact numbers of likes, dislikes and the like ratio, as seen on Figure 3.
- Are the internet search trends correlated with the incidence and mortality of COVID-19 in a particular country? Or is this more due to media clamor? Google Trends may be helpful in this analysis [13].
- How does the density and movement of people influence the incidence and mortality of COVID-19?
- What words are users worldwide searching for during the COVID-19 pandemic. The online software *Keywords Explorer* may be used for this study [17].
- When did people stop traveling and what influences them to maintain their social distancing? Recent data provided by *Apple* Inc. on their device travel patterns have been published online and may be useful [18].

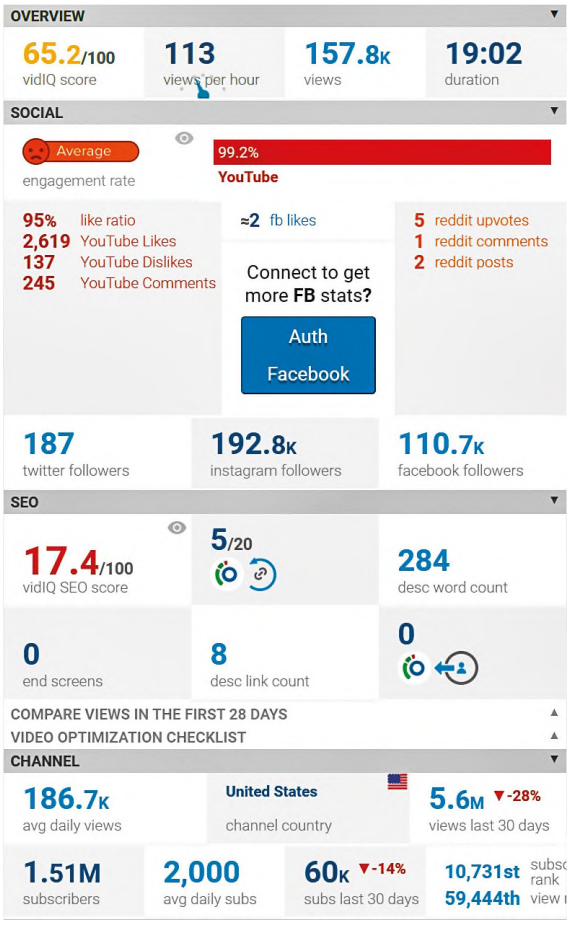

Figure 3: A screenshot of the statistics obtained from "vidIQ Vision for YouTube".

The data suggests that March 11, 2020 was the date that traffic in many European countries was officially restricted. This information may be correlated with media announcements.

- Online academic discussion forums like ResearchGate may offer additional new research ideas, links to datasets and an open discussion on various problems [19]. Data compiling initiatives such as Lens, provide an overview of information published on COVID-19 [20].
- The effectiveness of telemedicine in regards to COVID-19 treatment and treatment of other disease? [21,22].

Summary

Although several articles about COVID-19 are published daily, there are still several social, geographical and medical aspects which may be analysed. In this bioresource paper, we gathered relevant data concerning COVID-19 so that it is more convenient for researchers to analyse how the disease has developed over time. We hope that this bioresource paper and corresponding bioinformatics regarding the COVID-19 threat may encourage research, contribute to further understanding of epidemics, contribute to faster control of virus spread and help discover new scientific ideas.

Contact information

For those who are interested in scientific cooperation, who require an update to the database or who require help in realizing their scientific-oriented ideas may contact the corresponding author of this paper.

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