Inspire

INSPIRE
The Academy of Medical Sciences
Supported by wellcome trust

Volume 6 | Number 2 | Winter 2021-22

Student Health Sciences Research Journal

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MEDICAL | DENTAL | VETERINARY SCIENCES

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Student Health Sciences Research Journal

CONTACT
inspirestudentjournal@gmail.com

WEBSITE
www.inspirestudentjournal.co.uk

DESIGN
Cris Sutera
www.crissutera.co.uk

Welcome to the Winter 2021-2022 issue of the INSPIRE Journal: created by students for students

Hi! Welcome to the Winter 2021/2022 issue of the INSPIRE Student Health Sciences Research Journal. This issue has been written and peer-reviewed by students, with the editorial board being made up of students from the universities of Bristol, Cardiff, Exeter and Plymouth (the journal's founding institutes). The Inspire Journal was created as part of the INSPIRE scheme, which aims to provide students in medical schools across the UK with the opportunity to take part in research and to encourage them to incorporate it into their future careers.

As we write this today, the UK has just been informed that all COVID restrictions are soon to be lifted. Like much of the COVID guidelines we have been given, this fills many of us with mixed feelings. Of course, we wish for life to become 'normal' again, but we are also aware of the risks involved with this. Time and again we have heard about the dangers of saturating the NHS for patients who have COVID; however, we hear less about those who may not require a ventilator but whose medical needs have still been neglected owing to the pandemic. For example, in this issue we hear about how short-term delay in cardiac surgery has affected cardiac patients during the pandemic. Another relevant topic is vaccine uptake; with 71% of the UK now being fully vaccinated, we have one of the higher vaccination rates globally, whilst countries like Iraq and Liberia have a vaccination rate of less than 20%. Nonetheless, many UK residents have chosen not to have the vaccine for various reasons. In this issue, we also look at barriers to treatment uptake, using HIV as an example; you will see that many of the barriers to HIV prophylaxis also exist for COVID protection, such as accessibility issues, education and societal pressures.

Of course, although COVID has taken a main seat in medicine (and our lives) over the past few years, there are many other important areas of research that span the field of medicine, dentistry and veterinary science, some of these being included in this issue. In addition, the INSPIRE Research podcast continues to provide a platform to delve into key healthcare issues. Finally, our blog page (see https://inspirestudentjournal.co.uk/resources/) includes interesting updates in the field of health sciences. All of this can be accessed via our website and social media pages (see links below).

So, with that, we will leave you to enjoy this issue and explore all that it has to offer. We hope that you will find the content informative, interesting and inspiring! We also welcome you to join the us by becoming an author, peer reviewer or editor for the journal!

With best wishes,

The INSPIRE Student Health Sciences Research Journal Senior Editors

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FRONT COVER
The cover image is centred around the COVID-19 pandemic. The intention of this work was to produce a cohesive narrative surrounding COVID, as it has had a considerable impact on ourselves and everyone around us in some physical, mental and social form. The aim was to try and evoke some of the emotions that people may have felt during this past year.

Cover credit:
Concept: Lakhan S. V. A. Ajmeria (Year 5, Medicine, University of Plymouth)
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News

Clinical update on the pharmacotherapy of borderline personality disorder

Gaia Vetere
Year 3, Medicine, University of Exeter
Email: gv267@exeter.ac.uk

Abstract

Patients with borderline personality disorder (BPD) are currently managed with psychotherapy and symptom-targeted prescribing, usually leading to polypharmacy, which is against the current NICE guidelines. Research shows that most drug therapies currently used for BPD have no clinical benefit and that the side effects of these drugs may be harmful to patients. Some of the BPD treatments that require further investigation are mood stabilisers and antipsychotics. Other potential treatments, such as omega-3 fatty acids/food supplements and oxytocin should also be investigated. NICE guidelines should be updated following further study.

Abbreviations

APA - American Psychological Association
BPD - Borderline personality disorder
CSF - Cerebrospinal fluid
EUPD - Emotionally unstable personality disorder
RCT - Randomised controlled trial

Introduction

Emotionally unstable personality disorder (EUPD) is a disorder of mood experienced by 20% of psychiatric in-patients and 10-30% of outpatients.[1] It can be caused by a genetic predisposition and/or an environmental cause.[2] These patients form their identity around an extremely traumatic childhood and this causes them to have a very different way of perceiving and interacting with the world around them.[2] There are two types of EUPD: impulsive and borderline personality disorder (BPD). The latter will be the focus of this paper.

> *BPD is characterised by a disturbed self-image, self-harming, fear of abandonment, emotional instability and, hence, an inability to form stable relationships.*[3]

These symptoms vary for every patient, especially since EUPD patients have other psychiatric disorder comorbidities. This makes it difficult to isolate which disorder is responsible for the presenting symptoms, hence diagnosis and treatment vary too.[4] To complicate things even more, there is contrasting evidence and different guidelines concerning the way BPD should be managed.[5-8] As a result, there are no clear guidelines to be followed and BPD patients are often on polypharmacy.[4]

The aim of this clinical update is to evaluate the current research and guidelines and to explore the pharmacological management of BPD. It will address the lack of research on the topic and the disparity between guidelines and practice. Lastly, it will highlight some fields for future research.

Current guidelines vs clinical practice

According to the NICE guidelines and the NHS website,[2,7] the main treatment for BPD should be individual or group psychotherapy. It is likely that this choice was made on the evidence for psychotherapy's positive effects on BPD patients and in not causing side effects.[6] The NICE guidelines emphasise that pharmacotherapy, especially polypharmacy, should be avoided unless the patient is comorbid; in this case, they approve giving medication for the comorbidity. In

contrast, the guidelines of the American Psychological Association (APA) recommend personalised therapy using a symptom-targeted approach.[8] Surprisingly, these guidelines have not been reviewed since 2009 and 2001, respectively. Although novel research is limited, enough new papers exist to motivate a review of these guidelines.

A national audit published in 2015 on the use of psychotropic drugs in patients with EUPD illustrates the reality within clinical practice in contrast to the guidelines.[4] In this study, of 786 patients who had EUPD without comorbidity, only 13% had not been prescribed psychotropic medication. In addition, two-thirds of the same patient group had polypharmacy aiming to target different aspects of EUPD, such as depression, anxiety and disturbed sleep. This shows that

> *the current approach in British hospitals follows the APA guidelines rather than the NICE guidelines for the NHS,[4] which emphasises the need for the NICE guidelines to be reviewed.*

Moreover, this audit found that the most prescribed classes of drugs were antidepressants and antipsychotics. Interestingly, several recent systematic reviews show that there is not enough evidence to support the use of either in BPD and noted that certain antipsychotics, like olanzapine and asenapine, might even be counterproductive in BPD patients due to their well-known side effects.[5,9] As a result, the audit findings may suggest that some BPD patients are being overmedicated,[4] and the lack of evidence for the medication that they are receiving makes one wonder if this is doing them more harm than good. This highlights the need for further research to evaluate the use of pharmacotherapy for BPD.

Update on the treatment of BPD and controversies

In the early 2000s, some promising papers were published on the use of mood stabilisers or antipsychotics in BPD.[10,11] The NICE guidelines even followed up on this by encouraging further research to strengthen the proposed clinical relevance of these drugs.[7] As a result, more studies looked into this[5,9] and found conflicting results to the previous studies.[10-14] The general consensus was that

> *more thorough research was required to establish a link between mood stabilisers/ antipsychotics and improvements in BPD outcomes.*

With regard to antipsychotics, a study found that BPD patients may have higher concentrations of dopamine metabolites in their plasma and cerebrospinal fluid (CSF), suggesting that some antipsychotics might have a positive effect on BPD since they target the dopamine pathway.[12] In particular, aripiprazole, olanzapine, haloperidol and quetiapine occasionally resulted in a positive response in previous studies.[12-14] However, many also reported side effects, especially with olanzapine, and questioned the reliability of the research on the topic, usually for methodological reasons or simply for the lack of further evidence.[5,9] Indeed, as seen in a recent systematic review,[5] most of the positive findings with antipsychotics has come from research conducted before 2010, none of which provides overwhelming evidence that would support the use of these drugs in BPD, hence its exclusion from current guidelines. To illustrate the issue, the case of aripiprazole can be used as an example: there is one placebo-controlled randomised controlled trial (RCT) on aripiprazole in BPD patients,[11] which reports an improvement in several symptoms of BPD (depression, anxiety, hostility, paranoia and psychoticism) and considers this treatment a safe and effective option. However, this paper was published in Austria in 2006 and included 57 BPD patients only, five of whom dropped out. Furthermore, patients with suicidal ideation, schizophrenia, and users of psychotropic drugs or psychotherapy were excluded, even though one might argue that, in the clinical reality of BPD, all of these presentations are fairly common.[1,4] The findings from this RCT have not been supported by any other research.[9] In conclusion, due to methodological limitations, there is a risk that these results may be inaccurate and, hence, they would need to be confirmed by further research.

With respect to mood stabilisers, a 2015 Cochrane collaboration reported that there has been past evidence of lamotrigine and topiramate occasionally reducing anger and impulsivity in BPD patients,[9] although the sources of this evidence were of questionable reliability. In particular, the Cochrane collaboration commented on two small placebo-controlled RCTs that found lamotrigine to improve anger and impulsivity in BPD patients.[15,16] In contrast, a double-blind placebo-controlled RCT published later, in 2018, showed that lamotrigine had no statistically relevant effects in a large group of BPD patients recruited from six different places in the UK.[17] This last study was carried out over 52 weeks and comprised of three follow-up periods, as opposed to the previous studies, which lasted less than 12 weeks.[15,16] Furthermore, the 2018 study[17] was more inclusive of patients with more severe BPD symptoms, whereas the two earlier studies excluded people who self-harmed, were unemployed, etc.[15,16] Hence, it becomes evident that the 2018 study has better methodology, which makes it more reliable and representative of the patients that would actually present in the clinical setting. Lastly, to explain the different results between these studies, it has been suggested that lamotrigine might be more likely to be effective for patients who have milder BPD symptoms.[17] Surprisingly, despite these mixed findings, the NICE guidelines still show interest in the use of mood stabilisers in BPD patients (although they would like further research on the topic), and a portion of BPD patients are receiving this treatment despite the absence of evidence to support its use.[4] This shows once again that further research and up-to-date guidelines are needed.

On a more positive note, some new unconventional therapies have been identified for BPD. The first of these are omega-3 fatty acids;[18,19] a recent study was carried out on 43 BPD outpatients, 18 of whom initially received omega-3 fatty acids and a mood stabiliser (valproic acid), and the remaining received valproic acid alone.[19] Both groups showed improvements after 12 weeks, especially in terms of anxiety, depression and social functioning. Moreover, the group that received omega-3 fatty acids and valproic acid showed less impulsivity, anger outbursts and self-injury. Subsequently, both groups took valproic acid alone for 24 weeks. At the end of the experiment, the group who had initially received combined therapy still showed reduced anger outbursts. Although this was a small study and did not include a placebo-controlled group, it did not find any serious side effects to the use of omega-3 fatty acids for BPD and cited appropriate research to support its findings. In conclusion, these results suggest that omega-3 fatty acid supplements show promise as a future treatment option in BPD, although further research will be needed to confirm this. Moreover, since psychiatric patients are known to have quite imbalanced diets, it might be interesting for future research to look into other food supplements and whether they improve BPD symptoms. Finally, despite the promising results, further research may be needed regarding valproic acid as a therapy, since its use in BPD is not backed up by any other evidence.

Another potential pharmacotherapy for BPD is oxytocin. A recent systematic review confirmed that oxytocin inhibits threat hypersensitivity and avoidance in BPD patients.[20] However, patients who received oxytocin were less trusting of others in a social dilemma.[20] Moreover, a correlation between childhood trauma and increased response to oxytocin was found,[21] which will have clinical implications if oxytocin is implemented in the care of BPD patients. In conclusion, the findings relating to oxytocin therapy for BPD are promising but further research is needed to understand the

contraindications of this therapy and the circumstances in which oxytocin could be beneficial for BPD patients.

Conclusion

EUPD/BPD patients are currently being managed with psychotherapy and symptom-targeted prescribing, usually leading to polypharmacy, which is against the current NICE guidelines. Research shows that most of the current drug therapies have no clinical benefit to patients and the side effects can actually be harmful. However, it also suggests that some treatments can be used in very specific circumstances.

These findings need to be reflected in the NICE guidelines. Some treatments that require further investigation are mood stabilisers and antipsychotics. Other potential treatments that require further research are omega-3 fatty acids/food supplements and oxytocin.

Acknowledgements Benjy Bailey (University of Exeter, Exeter, UK) is acknowledged for proofreading this article.

Contribution statement Gaia Vetere was the only author and contributor to the paper.

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Education & Teaching

Incorporating medical leadership and management into the undergraduate medical curriculum

Rahul Winayak
Year 3, Medicine, University of Bristol
Email: ob18537@bristol.ac.uk

Abstract

Medical leadership and management (MLM) is an underexposed area of the undergraduate medical curriculum. Refining the medical curriculum to clearly incorporate MLM is challenging, with barriers including a lack of staff experience and an already overcrowded curriculum. Frameworks such as the Medical Leadership Competency Framework (MLCF), break down MLM into five key domains, making it easier for medical schools to thoroughly incorporate teaching in this field into the undergraduate curriculum. It is crucial that MLM is incorporated at an early stage in medical students' careers so that we can become safe and competent doctors in the future.

Abbreviations

CBL - Case-based learning
FMLM - The Faculty of Medical Leadership and Management
GMC - General Medical Council
MLCF - The Medical Leadership Competency Framework
MLM - Medical Leadership and Management
MSF - Multi-source feedback
QIP - Quality improvement project
SSC - Student selected component

Introduction

Training in medical leadership and management (MLM) is vital for becoming a safe and competent doctor. Leaders pave the path for others to follow, inspiring them to do so as well. Leadership is quoted as 'getting results with and through people'.[1] Indeed, leaders would not exist without colleagues, and vice-versa. As emphasised in the General Medical Council (GMC),[2] doctors are part of multidisciplinary teams, so we must listen to and respect each member's opinion. In doing so, we will be driving forward healthcare and making a positive impact to patients' lives. It is, therefore, crucial that MLM is incorporated at an early stage in our careers, and I shall be offering ideas as to how this can be achieved.

Literature search

To assess MLM teaching in the current undergraduate medical curriculum, a literature search for primary research papers was conducted in January 2021 using PubMed. The following keywords were used to find papers: 'leadership', 'management', 'UK medical curriculum' and 'teaching'. The prerequisites for the selection of papers included that articles were specific to the UK medical curriculum and that full text was available. Google was used as a search engine to find websites for current MLM frameworks and guidance.

MLM in the current curriculum

Whilst medical schools nationally agree on the importance of MLM, little has been done to thoroughly integrate it into the undergraduate curriculum. Analysing over 70% of medical schools nationally, Jefferies *et al.*, (2016) conducted the first nationwide assessment of MLM in the undergraduate medical curriculum, which produced

data representative of UK medical schools.[3] They reported that 88% of medical schools aimed to increase MLM education but struggled to design teaching methods. This was, in part, due to an overcrowded curriculum, but also because of a lack of clear guidance on teaching methods at the time. Furthermore, as shown by Stringfellow *et al*., (2014), only 20.4% of students felt that they were being taught MLM correctly.[4] Crucially, while it does exist as part of the curriculum (mainly through lecture-based teaching), students feel session objectives are not clear or signposted well enough and would prefer more experiential learning.[3] As a result, The Faculty of Medical Leadership and Management (FMLM) devised a standardised curriculum relating to MLM education for medical schools to follow.[5]

Based on the Medical Leadership Competency Framework (MLCF), the curriculum draws on five key domains of leadership. The FMLM suggested that medical schools create opportunities in the darker shaded domains shown in **Figure 1.** These domains offer a greater range of opportunities for incorporation of MLM in the curriculum, and as such are discussed further below.[6] 'Setting direction' has been excluded from discussion as this domain draws on aspects of MLM on an organisational level, and so is less skill-based than the other domains.[5]

Figure 1. The MLCF. The figure has been adapted from the FMLM[5] and illustrates five key domains of MLM. The domains that are coloured blue can be incorporated more easily in the undergraduate curriculum.

Personal qualities

Attributes such as resilience, curiosity and self-awareness prevail among good leaders. Whilst most medical students may already possess these, the curriculum should be designed such that they are nurtured. Activities such as small group discussion using Balint format aid self-reflection and the critical appraisal of leadership skills amongst clinicians.[7] This is typically conducted in a small group setting where participants can describe particularly challenging cases, and the chair can lead the others through the processing of any thoughts or feelings that may arise. Personal experience has shown that, whilst uptake for these sessions may be low initially, due to the demands of clinical placement, students may progressively subscribe to the notion as they begin to encounter challenges in their clinical placement. Meanwhile, curiosity may be kindled at an earlier stage by allowing younger medical students to attend postgraduate lectures on topics they find interesting, which they could then follow up in a Student Selected Component (SSC) or an intercalated degree.

Working with others

Perhaps one of the most important aspects of MLM education involves medical students working effectively in any team. Attendance at multidisciplinary team meetings should be made compulsory during the clinical years so that students can observe members roles and team working dynamics.[5] Students should be encouraged to take minutes during meetings, as well as assisting foundation doctors in notetaking during ward rounds, making them feel more involved. Furthermore, students have the privilege of more time than doctors to listen to any worries or concerns patients may have and can communicate them with the clinician in charge.[5] Simultaneously, students can make patients feel more valued, and improve overall patient care, whilst nurturing their own leadership skills. However, as it may be overwhelming for students to assume a leadership role in a clinical setting, such roles should primarily be encouraged to students in clinical years.

Working with others should also be encouraged at an earlier stage, before clinical years. Team-building exercises should be incorporated more frequently, early on in the curriculum. This is a fun way of getting to know fellow peers and assists in identifying students who might lack the natural leadership qualities. These students could be asked to chair case-based learning (CBL) sessions more frequently, to build their confidence in a leadership role. CBL sessions are a form of regular group-based exercise where students learn through the discussion of cases, with a Chair to lead the session and a scribe to note down what was said. As shown by Quince *et al*., (2014), medical students believe feedback is an important way of both teaching and assessing MLM.[8] Notably, they claim that feedback is often 'asymmetrical' as students are required to give feedback and are hardly on the receiving end of it. Multi-source feedback (MSF) should be implemented early on in the curriculum, ensuring students receive feedback from tutors, peers and patients. This could be routinely incorporated after CBL and group simulation exercises.[5]

> *By ensuring regular mutual feedback, students will be encouraged to contribute more to group exercises and can target specific areas to improve their leadership qualities.*

Doctors work in multi-disciplinary teams, and so there should be a greater emphasis on interprofessional education. Lectures should be delivered by a wider range of professionals, and the curriculum should involve several interdisciplinary events, such as events including medical and engineering students.[5] Organisations like the MedTech Foundation host innovation programmes where medical students work alongside engineering and business students to create solutions to clinical problems.[9] Medical students should be encouraged to take part in these, to further their leadership skills, whilst embracing future collaboration and innovation within healthcare.

Managing and improving services

Whilst medical students are not required to undertake an audit or quality improvement project (QIP), the GMC stipulate in their learning outcomes for graduates that newly qualified doctors must be able to describe the principles of quality improvement and apply them to improve practice.[10] Aside from competencies, getting involved in audits and QIPs as a medical student will help in a number of other ways. For career progression, it allows students to demonstrate dedication to a speciality and offers the ability to network and collaborate with more senior clinicians. Furthermore, it equips medical students with the skills and knowledge needed later in their training (e.g., junior doctors are required to undertake a minimum of one audit annually).[11]

> *As opportunities to get involved in audits and QIPs are scarce, students should be offered formal teaching in these areas.*[4]

This will help to improve their confidence in audit methodology and can be followed up in formative assessments.[5] An example of where this is already happening is at Imperial College London, where students are required to undertake a QIP.[4] However, in an already saturated curriculum, lectures and assessment on this topic may not be seen as a priority by all medical schools. Therefore, SSCs in MLM should be offered, allowing more students to get involved in audits with clinicians. This is already being seen at Barts and The London School of Medicine and Dentistry where they have also created an MLM student society but should be standardised across the UK undergraduate medical curriculum to allow students to improve their management skills.[12]

Conclusion

Refining the medical curriculum to clearly incorporate MLM is challenging, with barriers including a lack of staff experience and an already overcrowded curriculum. Medical schools across the country differ substantially in teaching style, with some offering more traditional lecture-based teaching and others more integrative teaching, such as CBL.[13] Therefore, incorporating a standardised curriculum for each medical school to follow may prove challenging. Rather, medical schools should evaluate their current MLM teaching and devise strategies to bolster them further by using the advice given by the FMLM as well as student feedback.

Acknowledgements Thank you to the peer reviewers and editors whose feedback helped with editing this article.

Contribution statement The author made substantial contributions to the conception or design of the work, drafted the work and gave final approval of the version to be included in Inspire.

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Opinions

Not as simple as great experience: student volunteers in research

Daisy Campen
Year 4, Medicine, University of Exeter
Email: dc534@exeter.ac.uk

Abstract

The Coronavirus 19 (COVID-19) pandemic disrupted medical education as we know it. My personal experience volunteering with a coronavirus vaccine research trial prompted me to reflect more broadly on the involvement of medical students in research. In this article I will discuss the benefits I recognised during my experience of assisting with a coronavirus vaccine trial. I will also consider the benefits and issues that can arise from the involvement of medical students in research. The recent removal of points for Educational Achievement from the Foundation Programme Application process eliminates recognition of student accomplishment in research. Widening access in medical education is an important issue and currently students from less privileged backgrounds could be disadvantaged by being unable to take part in unpaid research projects. Student involvement in research is broadly beneficial but the potential inequalities in access to opportunities need addressing.

Abbreviations

COVID-19 – Coronavirus-19
CV - Curriculum vitae
FPAS - Foundation programme application system
NHS - National Health Service
MDT - Multi-disciplinary team

Introduction

In March 2020 hundreds of medical students across the country were sent home due to the worsening Coronavirus-19 (COVID-19) pandemic. COVID-19 is an infectious disease which results in respiratory illness, a pandemic was declared by the World Health Organization on March 11, 2020.[1] With 3,000 final year students graduating early to support the NHS, junior students were at home navigating online learning. Some students took on roles in community volunteer groups and some returned to jobs within the NHS.[2,3] By autumn medical students were able to return to university now designated as essential workers.[4] I was lucky enough to volunteer with a coronavirus vaccine study. Reflecting upon the experience I questioned the benefits and complex issues around medical students volunteering in research.

The benefits

Medical students have high levels of prosocial motivation which means they are motivated by acting to benefit others.[5] Higher levels of prosocial motivation predict more frequent volunteer behaviour, this is also influenced by the students' feelings of social responsibility.[5] When the opportunity to volunteer for a coronavirus vaccine research trial arrived, I was eager to take part. Being involved with the fight against the pandemic provided me with a much-needed morale boost. It was a welcome change after six months of disrupted placements and online learning. I was able to hone my clinical skills in venepuncture and develop my communication skills by meeting the trial participants. I had the opportunity to work in and learn from a multidisciplinary team (MDT) with research nurses, doctors, and healthcare assistants.

> *The use of students in the role of research assistants meant that staff were free to work on the wards of the hospital.[6]*

Another benefit was an improved understanding of how a large-scale randomised control trial operates. I was required to undertake Good Clinical Practice training.[7] Through this I learnt about the importance of informed consent during research and the logistics of implementing the trial.

More generally, medical students can undertake their own research as part of the curriculum or by participating in a project at their university. This provides an opportunity to explore a topic of interest in further detail. Students develop skills in critical appraisal and critical thinking which may result in long-term research productivity.[8] Students can then publish their findings or present at conferences. These experiences are highly regarded on curriculum vitaes (CVs) and can benefit the student during applications. Students can be involved in research studies during data collection, this is beneficial for them as they make connections with researchers. It is also valuable to the research team as medical students will often volunteer their time, are flexible with working hours and eager to be involved due to their high levels of prosocial motivation.

The issues

Medical students are busy, balancing clinical placements and independent study; therefore, finding time to volunteer can be challenging. In guidance published by the Medical Schools Council they state that a student's priority should be their education and they should not undertake additional responsibilities that could jeopardise their ability to graduate.[9] However, getting the balance right is difficult, especially with the pressure of wanting to gain CV enhancing experiences. This could result in some students overburdening themselves and their education suffering.

Furthermore, medical students come from diverse backgrounds with some also having to balance paid employment. A small Australian study showed that students from widening participation backgrounds may have unique financial challenges and are more likely to undertake part-time employment.[10] Anecdotally medical students' involvement in research is often voluntary, and they are rewarded with the experience. For students juggling employment it can be challenging to justify voluntary work, which could leave them disadvantaged regarding research experience.

> *The announcement that points for Educational Achievement will be removed from the Foundation Programme Application System (FPAS),[11] has de-incentivised publishing research. This raises the question of why medical students would take part in research.*

Although a variety of experiences are useful for interviews and later speciality training, they seem a distant prospect to most medical students. The British Medical Association worries that this announcement will have long term implications, with students not fostering their inquisitive nature through research.[11]

Conclusion

It is clear that medical student involvement in research has many benefits to the student and their future engagement with research. Nonetheless, there are some issues around voluntary research work, as this may exclude less privileged students from being able to undertake the same experiences as their peers.

> *This is why the inclusion of a research projects within the core curriculum is so important as it provides the chance for all students to take part in research regardless of their background.*

The removal of points for publication from the FPAS leaves medical students with little immediate reward for their engagement with extra-curricular research. Further research should be undertaken on the relationship between students from widening participation backgrounds and their ability to take part in research. This could identify an area where medical schools could offer support thus improving equal opportunities for all medical students.

Contribution statement The author confirms that they were the sole contributor to the conception, drafting and revision of this work, and the author approves the final version to be included in Inspire.

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Opinion

A journey through time in global surgery

Joana Letícia Spadoa

Year 4, Medicine, Universidade Federal de Ciencias da Saude de Porto Alegre
Email: leticiaspadoa@gmail.com

Abstract

According to the 2015 Lancet Commission report, 5 billion people do not have access to necessary surgical care around the world. Global surgery was born to solve this problem, being a field of study, research, practice, and advocacy that aims to improve health outcomes and achieve health equity for all people who need surgical, anaesthesia, and obstetric care. This idea emerged more than 40 years ago and resulted in very interesting initiatives in favour of better surgical care, evolving together with global health. Currently, global surgery has received the engagement of medical students worldwide, being a fundamental topic in the formation of these future health professionals. Therefore, the purpose of this article is to reflect on the past, present and future of global surgery, drawing a parallel with the story of the protagonist of the book series Outlander, by Diana Gabaldon.

Abbreviations

DALY - Disability-adjusted life year
HIC – High-income countries
LMIC - Lower-middle-income country
WHO - World Health Organization

Background

In Outlander by Diana Gabaldon, the protagonist Claire, a World War II combat nurse and then a surgeon who travelled through time, faces the challenge of applying her twentieth-century surgical knowledge, including anaesthesia, antibiotics, and antisepsis, to the less-resourced scenario in eighteenth-century.[1] Thinking otherwise, if Claire were supposed to travel to the twenty-first century, how would she practice medicine with all the current surgical knowledge?

In the sixth book of the series, the character identifies a serious condition called persistence of the ductus arteriosus in her newborn granddaughter, which required surgical treatment. However, unfortunately, she was unable to solve this problem in the eighteenth century. Today, just like Claire's granddaughter, a newborn with a congenital malformation, or other patients who need appropriate surgical care, such as a mother in labour, a man with appendicitis, a woman with breast cancer, or an elderly person with a bone fracture, may not be dealt with adequately in many countries, leading to disability or death. Back to Claire, if she were to travel to the twenty-first century, she would be disappointed to see that despite the current evolution in surgical care, many people do not have access to necessary surgery, which is what she faced in the 1700s but in a different context. However, global surgery has been born to solve this problem.

The past

Conceptually global surgery is a field of study, research, practice, and advocacy that aims to improve health outcomes and achieve health equity for all people who need surgical, anaesthetic, and obstetric care, focusing on underserved populations and populations in crisis.[2] This idea started in 1980 with a remarkable speech from the Director-General of World Health Organization (WHO), Dr Halfdan Mahler, in the World Congress of the International College of Surgeons. He pointed out the relevance of surgery as a public health issue, emphasised the lack of access to surgical care for the majority of the world's population and asked for solutions.[3,4] More recently, a breakpoint was the establishment of the Lancet Commission on Global Surgery in 2014, an initiative that has significantly leveraged global surgery, especially with its report stating evidence and solutions for improving surgical care by 2030.[2]

> *Thus, although global surgery and global health have always walked together, nowadays they are inseparable.*

The present

When discussing global health, it is essential to recall the WHO Constitution's moral principle: "the enjoyment of the highest

attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition".[5] Unfortunately, surgical care does not meet this principle. According to the 2015 Lancet Commission report, 5 billion people do not have access to necessary surgical care.[2] In low-income and lower-middle-income countries (LMICs), nine in ten people cannot access basic surgical care.[2] As a consequence, surgery is responsible for about 30% of the global burden of disease.[2,6] The outcomes are sad: with the lack of an accessible and safe surgical system, people may die from avoidable conditions or cope with the consequences for a prolonged period of time. With this perspective, it is estimated that

> *scaling up basic surgical care in the health system in LMICs could prevent 1.4 million deaths and 77.2 million disability-adjusted life years (DALYs) per year.*[7]

Therefore, global surgery is a matter of guaranteeing a healthy life for our world's population, as the WHO Constitution intended.

Moreover, when considering global surgery in 2021, it is essential to mention the COVID-19 pandemic's impact on surgical systems. According to the predictive model made by the CovidSurg Collaborative, in a disruption period of 12 weeks because of COVID-19, more than 28 million operations would be cancelled or postponed, with 37.7% of those procedures being operations for cancer.[8] In many countries, the pandemic forced the surgery system to slow down in pace, which may have worsened previous problems, especially in LMICs. Nonetheless, there are solutions for this issue: improving surgical systems can help to build capacity for the treatment of patients during a health emergency, like the COVID-19 crisis.[9] Thus, investing in surgery can help to ensure preparedness for pandemics, as clearly addressed by Dr Key Park in the ARU Surgical Society Global Surgery Symposium. Hence, it is crucial to include this topic on the global surgery agenda from now onwards.

The future

Thinking towards the future, global surgery may be a fruitful tree, the seed of which we plant today. A pivotal step is to invest in people who are the future of the operation room. For that, universities around the globe, especially outside of high-income countries (HIC), must include global surgery in their medical curriculum. Students must discuss this topic in classrooms and, in turn, aim to improve their local surgical system. Likewise, surgical societies must promote mentorship programmes to facilitate a relationship between surgeons and trainees interested in global surgery. Furthermore, it is important to set up a culture of searching, discussing and producing scientific literature at all academic stages to investigate, assess and find solutions to global surgery. An example is the InciSioN initiative, a non-profit organisation comprised of students, trainees, and early career physicians around the world, dedicated to advocacy, education, and research on global surgery.

To summarise, "partnership" would be the keyword for Claire's travel to the future of global surgery. Since global surgery began, HICs lead most initiatives in this field. However, global problems demand global solutions. It is fundamental to establish a collaboration between the most diverse agents in global surgery. We must give voice to those who most need surgical care. For this, social media can be a catalyst tool for a worldwide network in global surgery. Sharing a personal example, even as an undergraduate student, I feel connected with a community of people interested in global surgery—people that try their best to improve the surgical systems around the world. In that network, I know Claire would be very willing to contribute.

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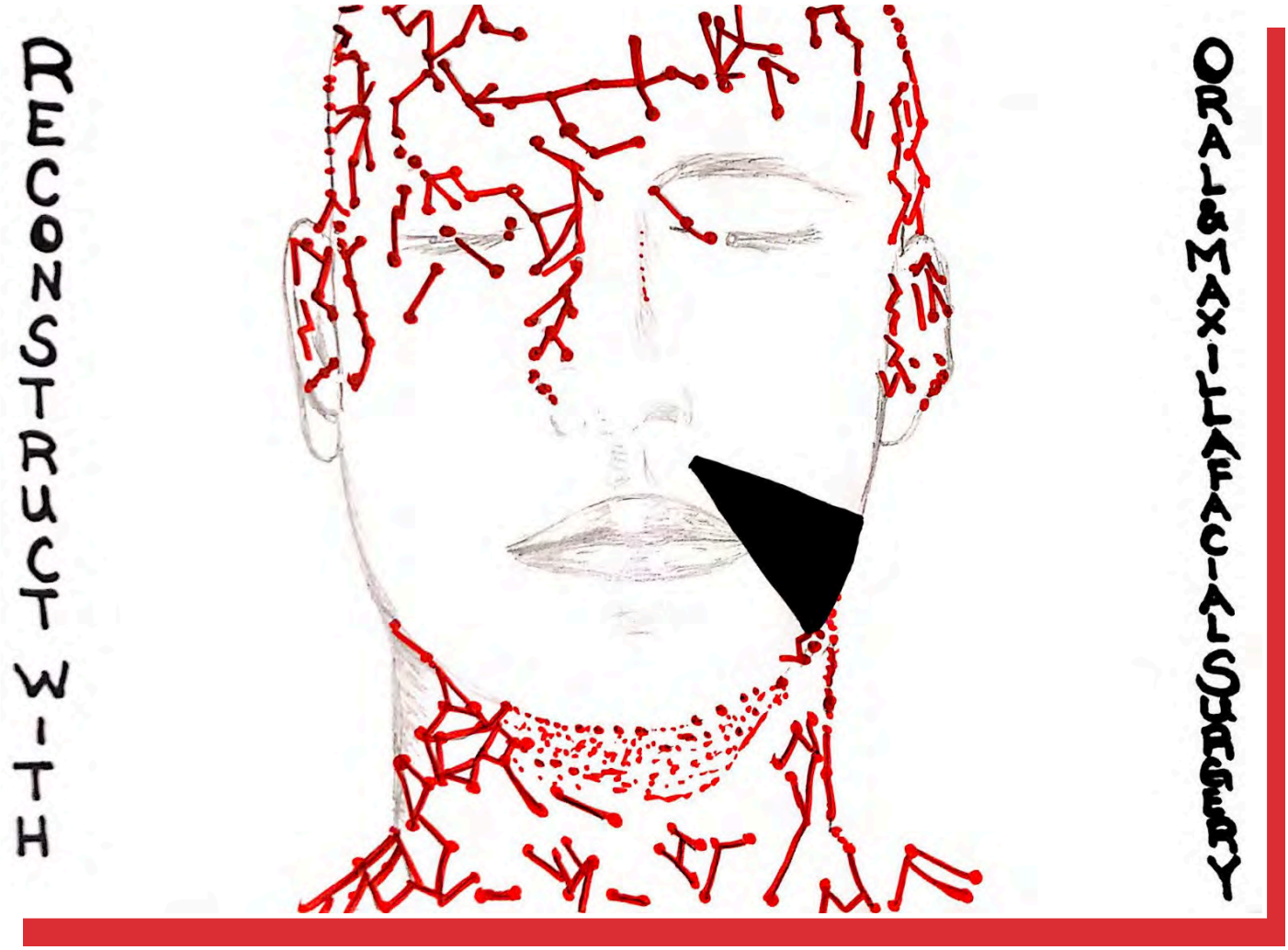
Competition

Cardiff Uni ersity Surgical Society's Art and Poetry Competition 2021: Oral and Maxillofacial Surgery: Where Medicine Meets Dentistry

In April 2021, the Cardiff University Surgical Society conducted an Art and Poetry competition in collaboration with the *Inspire Student Health Sciences Research Journal*. We are pleased to present the winning piece, which was illustrated by Saniyeh Zahra, a 3rd year dentistry student at the Medical University of Plovdiv, Bulgaria:



Saniyeh states, 'the idea behind the sketch is that all the nerves are the building blocks of the face and the triangular area represents a defect which dentists and doctors come together to overcome and treat to restore the full function of the face; almost like completing a jigsaw with its final piece to form a perfect picture.'

Review

What is the evidence that saliva is a suitable alternative to serum in the diagnosis of systemic disease? A review of the literature

Liam Fletcher
Year 4, Dentistry, University of Bristol.
Email: oj18783@bristol.ac.uk

Abstract

The need for rapid, reliable diagnostic methods has never been more evident in the light of the COVID-19 pandemic. Salivary diagnostics are a non-invasive, quick and inexpensive tool in the detection of disease and their potential are yet to be fully harnessed. The aim of this review article is to assess the feasibility of using saliva as an alternative biological fluid to serum in the diagnosis of systemic disease. The objectives of this article were to: (1) identify if the physiological properties of saliva support its use in being able to reflect various physiological states of the body; (2) evaluate the current evidence with regard to the use of salivary biomarkers compared to conventional serum biomarkers in the detection of some of the most prevalent systemic diseases; and (3) establish whether current technology potentiates the clinical application of salivary diagnostics.

Abbreviations

AMI - Acute myocardial infarction
CTnI - Cardiac troponin I
ECG – Electrocardiogram
ELISA - Enzyme-linked immunosorbent assay
GCF - Gingival crevicular fluid
HIV – Human immunodeficiency virus
LFT - Lateral flow test
LOC - lab-on-chip
PCR – Polymerase chain reaction
POC - Point-of-care

Introduction

A diagnostic biomarker is a biological measurement that can be used to confirm the presence or absence of a disease and contributes significantly to modern-day diagnosis. Perhaps the most consequential benefit of diagnostic biomarkers is their ability to detect disease in the absence of physical signs and symptoms, removing the need to rely on these parameters alone. This, in turn, facilitates earlier diagnosis and, thus, earlier prevention or treatment, most importantly in diseases that exhibit late-stage presentation. In addition, diagnostic biomarkers have the potential to expedite clinical trials when used as a surrogate endpoint and pave the way to redefine the classification of a disease using biological measurements as opposed to physical characteristics.[1] The conventional method to identify diagnostic biomarkers in the body is via blood serum analysis, yet this requires an invasive method of collection and extensive training from the practitioner. Saliva has an array of biological functions and cannot be overlooked as a non-invasive, quick and inexpensive alternative diagnostic fluid[2,3] as it possesses an abundance of informative molecules for diagnosis, including DNA, RNA and proteins.[4] This review will investigate the evidence as to whether saliva can be utilised as an alternative to serum as a diagnostic tool for systemic disease by: (1) considering the properties influencing its diagnostic potential; (2) summarising our understanding of salivary biomarkers versus conventional serum biomarkers in three prevalent systemic diseases; and (3) discussing the feasibility of using saliva with current diagnostic instrumentation in a clinical setting.

Properties of saliva influencing its diagnostic potential

Saliva arises from a variety of sources including the major salivary glands and minor salivary glands. The extent of contribution of saliva from these sources varies depending on whether the saliva is stimulated or unstimulated (see **Table 1**).[5] Saliva production relies on a series of active and passive diffusion mechanisms (**Figure 1a**), which lead to a final product rich in protein, electrolytes and more (see **Table 1**).[6]

In the mouth, saliva is mixed with gingival crevicular fluid (GCF), which is the fluid around the necks of teeth (see **Figure 1b**). GCF contains cytokines, immunoglobulins, host enzymes, serum proteins and inflammatory cells. The contributions from GCF to the saliva occur via capillary leakage and provide dynamic, real-time information pertaining to biomolecules that can be found in serum.[7]

Salivary flow rates exhibit high intra- and interindividual variation due to factors like hydration status, age, disease and medication, with higher flow rates reducing and lower flow rates elevating biomarker concentrations.[8] For example, a 38% reduction in flow rate was observed in the elderly,[9] suggesting that concentrations of salivary biomarkers may be elevated in this cohort. This decline is often attributed to the physiological ageing process; however, polypharmacy and the presence of disease is more often the explanation. Thompson *et al*. established the link between polypharmacy and hyposalivation, with a number of medications having a severe effect on salivation. In a study of elderly people, participants were found to be taking a variety of drugs, including antihypertensives, antidepressants, analgesics, and statins. Hyposalivation was associated with use of antidepressants or bronchodilators.[10] Thus, considering that systemic disease is more prevalent in an ageing demographic, it is important to be aware that associations between salivary biomarker concentration and disease could be heavily affected by the reduction in salivary flow rate and volume variability. Consequently, caution is warranted when interpreting study data with regard to biomarker concentrations associated with disease, most notably with studies that do not account for age differences.

Salivary biomarkers associated with common systemic diseases

Cardiovascular disease Cardiovascular disease is one of the main causes of death globally. The burden of this disease is on the rise, with more than 5 million additional deaths reported in 2015 compared to 1990,[11] highlighting the need for rapid diagnosis to reduce mortality. The most preferable biomarker in serum for the diagnosis of acute myocardial infarction (AMI) is cardiac troponin I (cTnI), a protein released into the blood when the myocardium is damaged. Foley *et al*. reported that salivary cTnI levels exhibit a positive correlation with serum cTnI, yet consistently show lower concentrations.[12] The participants in the study by Foley and colleagues were chosen based on the fact that they were undergoing surgical intervention for heart disease (alcohol septal ablation or percutaneous coronary intervention). Therefore, cardiac damage would be largely influenced by surgical and human factors and, thus, may not accurately mirror the event of an AMI. Nonetheless, Mishra *et al*.,[13] who utilised participants suffering from AMI within 24 hours, reported a statistically significant elevation in salivary cTnI compared to the control, confirming that saliva can reflect cardiac damage. Despite the low concentrations of cTnI reported in both studies, there is evidence to suggest the concentration of this marker in saliva is sufficient for detection.[14] Furthermore, Floriano *et al*. investigated the use of a panel of 3 salivary-based biomarkers, consisting of C-reactive protein, myoglobin and myeloperoxidase, as a screening tool for AMI. This saliva-based biomarker panel was shown to have a sensitivity and specificity similar to serum diagnostics when used in conjunction with an electrocardiogram (ECG).[15] This study provides a good level of evidence according to the Oxford Centre of Evidence-Based Medicine (Level 2b, which is 'an exploratory cohort study with good reference standards').[16] The advent of highly sensitive tests potentiates the use of salivary cTnI in AMI diagnosis, yet the utility of a panel of biomarkers may offer the best diagnostic capabilities.

Diabetes An estimated 451 million adults live with diabetes, and this is projected to rise to 693 million by 2045. Diabetes is a major cause of cardiovascular, kidney and liver disease[17] yet, in the case of type 2 diabetes, is preventable and reversible in its early stages. Therefore, the need for early identification is paramount in facilitating early prevention. A diabetes diagnosis is confirmed by the detection of a fasting blood glucose of greater than 7 mmol/l or a two-hour postprandial plasma glucose concentration greater than 11.1 mmol/l.[18] Unstimulated whole saliva and serum glucose levels are shown to correlate, with higher concentrations being found in diabetic patients. One study reported that when a salivary glucose level is equal to or greater than 0.25 mmol/l, a diabetes diagnosis could be made with 78% sensitivity and 80% specificity.[19,20] Contrary to this, Wang *et al*. reported no correlation between unstimulated whole saliva and serum glucose levels, but did note an association between parotid gland-derived saliva and serum glucose.[21] Parotid gland synthesis of saliva fluctuates considerably, and saliva production is increased by 30% when stimulated vs unstimulated.[4] The variability in the extent to which parotid glad-derived saliva contributes to whole saliva may explain the differing results found regarding the association between saliva glucose and serum glucose, as well as casting doubt on the reliability of using a predetermined glucose value (as used with serum glucose) when using saliva to diagnose diabetes.

The scope of salivary diagnostics with regard to diabetes is yet to be expanded to include a panel of biomarkers, such as that suggested for the diagnosis of cardiovascular disease. Additional salivary biomarkers demonstrating a statistically significant elevation between diabetic and healthy patients include salivary amylase, calcium and phosphorus, all of which are potential candidates for the construction of a biomarker panel, which may provide more consistent and reliable diagnostic results.[19]

Human immunodeficien y virus Around 1 million people die every year because of an underlying infection with human immunodeficiency virus (HIV), with the majority being concentrated in sub-Saharan Africa.[22] Considering the greatest prevalence of HIV is within low-income countries, the availability of simple and cheap diagnostic tests is hugely beneficial. The use of saliva as a diagnostic tool for HIV forms the basis of one of the most successful salivary diagnostic tests, known as OraQuick. This test detect immunoglobulins against HIV in saliva that have passed from serum via oral mucosa transudation.[25] Belete *et al*. and Deville and Tempelman reported sensitivities and specificities of approximately 99% and 100%, respectively, when using OraQuick to diagnose HIV;[23,24] these validating cohort studies present a high level of evidence (Level 1b).[16] However, a study that included participants taking antiretroviral medication showed that the sensitivity of OraQuick is lower in cases with a reduced viral load, whilst blood serum analysis provided a constant sensitivity and specificity of 100% regardless of viral load,[26] maintaining its status as the gold standard for HIV diagnosis. A solution to this could be the utilisation of a panel of biomarkers, such as salivary malondialdehyde (a factor that is positively associated with oxidative stress, which is elevated in HIV-infected patients)[27] in conjunction with immunoglobins.

See **Table 2** for a summary of all biomarkers discussed in this review.

Application of salivary diagnostic instrumentation to clinical practice

Biomarkers can come in a variety of forms, including DNA, RNA and proteins. As such, an array of laboratory tests can be utilised to

Table 1. Sources of saliva. The physical properties and percentage contributions of saliva from its various sources.[5]

Source	Acinar type	Viscosity	Composition	Unstimulated saliva (%)	Change from unstimulated to stimulated saliva (%)[a]
Parotid gland	Serous	Watery	Amylase, proline- rich proteins, agglutinins, and small amounts of cystatins, lysozymes, and extraparotid glycoproteins	20	+30
Submandibular gland	Mixed (predominately serous)	Semi-viscous	All components of serous and mucous secretions, including high levels of cystatins	65	-
Sublingual gland	Mucous	Viscous	Mucin glycoprotein-1, mucin glycoprotein-2, lysozymes	7-8	-
Minor salivary glands	Mucous	Viscous	Mucin glycoprotein-1, mucin glycoprotein-2, lysozymes	10	-
GCF	-	Watery	Electrolytes, inflammatory mediators, cellular components, host enzymes, and metabolic and tissue breakdown products	<7	-

[a]Data for stimulated saliva is only reported for the parotid gland.

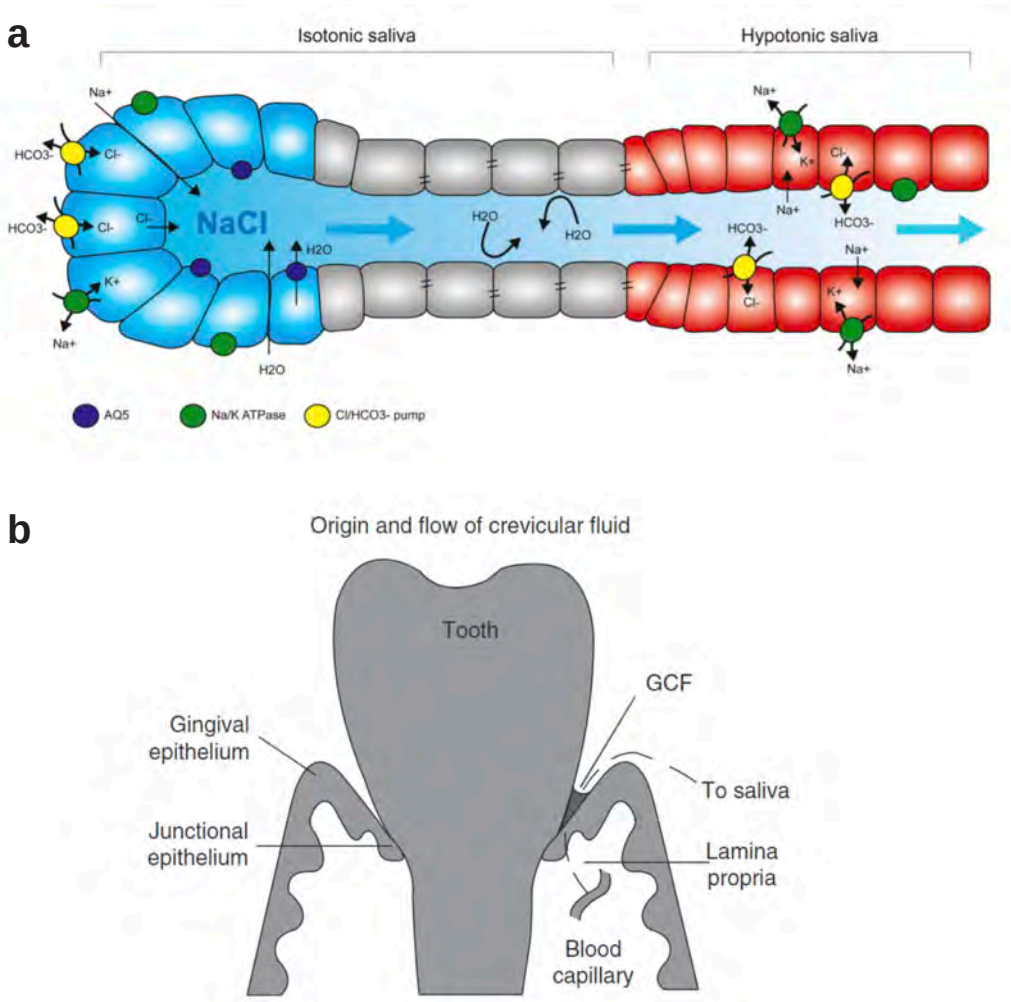


Figure 1. The stages of saliva production. (**a**) Saliva production begins with the formation of a primary isotonic saliva, containing sodium chloride (NaCl), via active and passive diffusion. This is subsequently modified and NaCl is replaced with bicarbonate (HCO_3^-) and potassium (K^+) ions, resulting in a hypotonic product. Figure from Porcheri and Mitsiadis.[7] (**b**) GCF is produced via transudation from the blood capillary, utilising transcellular and paracellular transport mechanisms, followed by passage through the lamina propria connective tissue and, finally, junctional and sulcular epithelium filtration into the gingival sulcus. GCF then passes to saliva. Reprinted from Challacombe *et al.*[6], with permission from Elsevier.

detect biomarkers, being specific for a given type of marker. Some conventional laboratory tests include polymerase chain reaction (PCR) and DNA/RNA sequencing, microarrays for measuring DNA, microRNA or protein analysis, culture techniques for the maintenance or growth of biological samples, and enzyme-linked immunosorbent assay (ELISA). ELISA is one of the most sensitive and omnipresent diagnostic tools in healthcare,[28] which can also be applied in salivary diagnostics. However, the biomolecules in saliva, most notably peptides, are susceptible to rapid degradation and require immediate processing or expensive requisites to preserve the sample in a clinical setting.[29] This renders methods for peptide analysis, such as ELISA, less preferable in clinical care. A range of point-of-care (POC) instruments have been identified with sufficient sensitivities for use in salivary diagnostics, such as the lab-on-chip (LOC) systems.[30] These systems possess one laboratory function or include several functions on a single integrated circuit, facilitating rapid results, thus making them more suitable for clinical application for salivary diagnostics. An example includes the lateral flow tests (LFTs) currently being used to detect the presence of SARS-CoV-19 during the COVID-19 pandemic (**Figure 2**). LFTs can be performed by patients and provide

Table 2. A summary of the salivary biomarkers for cardiovascular disease, diabetes, and HIV discussed in this article.

Salivary biomarker/ biomarker panel	Advantages	Disadvantages	Study authors; level of evidence[a]
Cardiovascular disease			
C-reactive protein, myoglobin and myeloperoxidase	• Excellent sensitivity and specificity (80-90%) when used with ECG	• Needs to be used in conjunction with ECG recordings to achieve optimum specificity and sensitivity	Floriano *et al.*;[15] Level 2b
cTnI	• Direct correlation with serum troponin levels • Established laboratory tests already in use for serum diagnostics	• Significantly lower concentrations compared to serum, making detection difficult • Tests with greater sensitivities required for confident diagnosis	Foley *et al.*;[12] Level 3b Mishra *et al.*;[13] Level 3b
Diabetes			
Glucose	• Potential correlation with serum glucose levels • Method of detection quick and easy	• Results heavily influenced by extent of saliva contribution by various glands • Glucose concentrations considerably lower when compared to serum	Ladgotra *et al.*;[19] Level 3b Mrag *et al.*;[20] Level 2b Wang *et al.*;[21] Level 3b
Amylase	• Significant elevation in salivary concentrations in diabetic patients compared to people without diabetes • Greater concentrations in saliva relative to serum	• Poor stability when not kept under optimum conditions due to enzymatic properties • Requires rapid processing	Ladgotra *et al.*;[19] Level 3b Mrag *et al.*;[20] Level 2b
HIV			
HIV-1/2 antibody	• Excellent sensitivity and specificity (99-100%) • Rapid testing kits already available (e.g. OraQuick)	• Viral load heavily influences sensitivity of salivary diagnostics, unlike serum diagnostics	Belete *et al*;[23] Level 1b Deville and Tempelman;[24] Level 1b
Malondialdehyde	• Accurately reflects oxidative stress in HIV-positive patients • Can be used in conjunction with antibody testing to strengthen diagnostic capabilities	• Insufficient evidence to be used alone	Amjad *et al.*;[27] Level 3b

[a]Level of evidence according to the Oxford Centre of Evidence-Based Medicine:[16] Level 1b, validating cohort study with good reference standards; Level 2b, exploratory cohort study with good reference standards; Level 3b, non-consecutive study or without consistently applied reference standards.

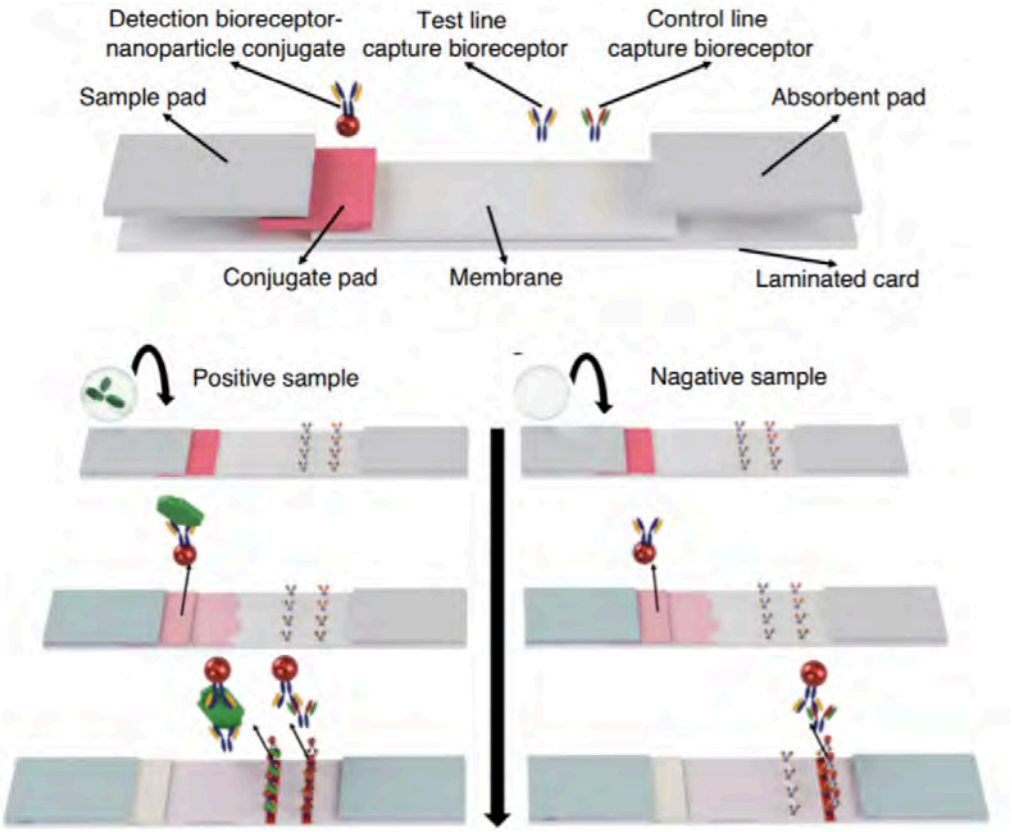


Figure 2. The mechanism of a LFT used to detect the presence of SARS-CoV-19 during the COVID-19 pandemic. The sample is placed onto the sample pad and works its way along the strip by the capillary action stimulated by the absorbent pad. Target analytes that are present bind to the immunofluorescent antibody on the conjugate pad. The combined target and antibody will travel along the nitrocellulose membrane and bind to a binding reagent. This produces a distinct fluorescent line on the membrane, with a darker colour corresponding to a greater concentration of the analyte. Adapted from Parolo *et al.*[31] by permission from Springer Nature.

rapid results, within 30 minutes. This removes the need for testing facilities and trained staff, thus reducing the overall expense and time consumption required for laboratory testing. Recent data reported by the Department of Health and Social Care presents an LFT sensitivity of 50.1% and specificity of 99.72-100%, while the sensitivity of PCR is 94.2-100% and its specificity is 100%.[32] Although the sensitivity of the LFT renders it inferior to PCR, its high specificity means that a positive result does not need to be confirmed with further testing, making it a useful screening tool when laboratory resources are scarce. Thus, it is evident that there are rapidly emerging diagnostic tools that pave the way for salivary diagnostics in the clinical settings upon the validation of appropriate biomarkers.

Conclusion

Salivary diagnostics offers less invasive sample collection methods and lower costs of procurement than blood diagnostics by circumventing the need for expensive training and laboratory testing. Modern technology offers unprecedented application of salivary diagnostics in clinical practice, with advents such as rapid LFTs, which have played an instrumental role in the diagnosis of COVID. The literature presents an abundance of possible biomarkers, with biomarker panels having the highest potential, with some tests having sensitivities and specificities comparable to that of blood serum, most notably for HIV diagnosis. It is suggested that the properties of saliva, such as high flow-rate variability, as well as the range of contributions from different saliva sources to the total saliva volume, both between and within patients, may be the main barrier to reaching a consensus on which salivary components may be useful biomarkers for disease. Consequently, it is likely that there are many salivary biomarkers that remain to be elucidated and further investigations should account for properties that may be confounding to the use of saliva for disease diagnosis. In addition, future research should focus on the identification of new salivary biomarkers, as well as those already identified, with large-scale trials and subsequent validation of findings before saliva can be utilised as a reliable alternative to blood serum in the diagnosis of disease.

Acknowledgements With special thanks to Dr Angela Hague (University of Bristol, Bristol, UK) who helped with editing this review.

Contribution statement The author conducted the literature search, drafted the review, and approved the final version for inclusion in Inspire.

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Review

Does buccal infilt ation efficacy change with articaine or lidocaine use in posterior teeth?

Rebecca Pullin[1] and Scott Kilpatrick[1]

[1]Year 4, Dentistry, University of Bristol
Email: beccaapullin@gmail.com

Abstract

Aims Lidocaine is the local anaesthetic (LA) solution most used in the UK. Debates that articaine is safer and a more effective alternative are ongoing. This review aims to assess whether adults undergoing posterior buccal infiltrations with either 4% articaine 1:100,000 adrenaline or 2% lidocaine 1:100,000 adrenaline experience greater anaesthetic efficacy.

Methods Medline, Cochrane and Web of Science databases were searched, using key terms including lidocaine, lignocaine, articaine, carticaine, compare, versus and infiltration to collect papers for the inclusion criteria. Both authors (RP and SK) evaluated the eligibility of each trial separately before assessing risk of bias.

Results Eight randomised control trials were included. Of these, seven trials were assessed to have high risk of bias and one was deemed unclear. Consequently, the data provided weak evidence to validate the hypothesis that adults undergoing posterior buccal infiltrations with 4% articaine 1:100,000 adrenaline experience greater anaesthetic efficacy than with 2% lidocaine 1:100,000 adrenaline.

Conclusions Current studies are too ambiguous to comprehensively conclude whether articaine or lidocaine solution provides greater anaesthetic efficacy, during posterior buccal infiltrations. Stronger evidence is required, dentists should remain aware of the limitations of different anaesthetics for a patient's safety and comfort.

Abbreviations

BDJ – British Dental Journal
EPT – Electric pulp tester
GDC – General Dental Council
LA – Local anaesthetic
PICO – Participant, intervention, comparison, outcome
RCT – Randomised controlled trial
ROBVIS – Risk of bias visual
VAS – Visual analogue scale

Introduction

Both articaine and lidocaine can be delivered by buccal infiltration, a commonly used technique for most clinical scenarios. Buccal infiltrations are advantageous as they are less technique sensitive for the operator and more comfortable for the patient. Fewer complications, e.g., nerve injuries are reported when administering buccal infiltrations compared to direct nerve blocks.[1]

When choosing between local anaesthetics (LA), certain characteristics need to be accounted for in order to choose the appropriate solution to administer on a case-by-case basis. Lidocaine is comprised of an amide group that is metabolised in the liver and has a half-life of ~2 hours so is preferable for patients undergoing longer procedures. Articaine has both an amide and an ester group which allows the LA to be metabolised by plasma cholinesterase in the blood, which decreases the half-life to ~0.5 hours.[2] The shortened half-life decreases the duration of action and so is beneficial for shorter procedures. This added medium for metabolisation also decreases the toxicity of articaine, though potential nerve paraesthesia should still be carefully accounted for.[3]

However, the wide availability of LA solutions makes it challenging for dental practitioners, when deciding which anaesthetic will be most efficacious. Efficacy summarises a local anaesthetic's performance by measuring properties that indicate anaesthetic success. These include

the number of patients achieving successful anaesthesia, pain during treatment and other secondary outcomes like pain on injection and onset of anaesthesia. Pain can be qualitatively evaluated by a visual analogue scale (VAS) where patients evaluate their own pain on a linear scale or by an electric pulp tester (EPT) where patients report any sensation felt from an electric stimulus applied to a single tooth.

The earliest review comparing articaine and lidocaine indorsed 4% articaine for simple dental procedures due to greater anaesthetic success and a comparable safety profile to lignocaine.[4] This recommendation was made despite finding that articaine may marginally cause greater post-injection pain.

More recent reviews have identified that anatomical differences could influence anaesthetic selection, when infiltrating posterior teeth, as both jaws are surrounded by dense cortical bone that could impede a local anaesthetic's diffusion.[5] Therefore, an ideal property of a local anaesthetic solution would be the ability to overcome this and provide a safe, reliable numbing effect.

There was a publication in the British Dental Journal (BDJ) in September 2020[6] indicating the need for this article. The current review aims to provide strong evidence as only randomised control trials will be used and a risk of bias will be generated for all included studies.

> *This systematic review aims to assimilate findings to advance best practice and answer the Participant, Intervention, Comparison, Outcome (PICO) question, 'In posterior buccal infiltrations, does 4% articaine or 2% lidocaine have greater anaesthetic efficacy?' (**Figure 1**).*

P Participant	Adult dental patients undergoing Buccal infiltrations in posterior teeth
I Intervention	4% articaine with 1:100,000 adrenaline
C Comparison	2% lidocaine with 1:100,000 adrenaline
O Outcome	Anaesthesia efficacy

Figure 1. The PICO question answered in this review.

Methods

Three databases were searched on the 17th of June 2020, including Medline (on OvidSP), Cochrane Library and Web of Science: Core Collection. These databases evaluated material from the following dates: 1946-present (Medline on Ovid), 1900 to present (Web of Science).

The following inclusion criteria were applied:

- Published in English.
- In adult populations (17+ years old, all genders, all ethnicities).
- On molars or premolars.
- On mandibular or maxillary teeth.
- Studies comparing 4% articaine vs 2% lidocaine (with 1:100,000 adrenaline).
- Studies using buccal infiltration as the only dental local anaesthetic technique.
- Studies undertaken for extraction, endodontic treatment, or simulated restorations.
- Randomised control trials (RCTs) and meta-analysis of RCTs were prioritised for review over observational or non-randomised studies. RCTs remain the 'gold standard' for establishing causality because they provide high-level evidence and reduced risk of bias if well conducted.

Two assessors (RP and SK) carried out the literature search, independently reviewed the inclusion criteria for papers using pre-determined data extraction tables (**Figure 2**). If discrepancies occurred, assessors would discuss until they both agreed to include or exclude the paper in question. If no agreement was reached, a project supervisor was consulted. Risk of bias was assessed in all included studies as high, some concerns or low, using the Cochrane Risk of Bias (ROBVIS) tool.[7]

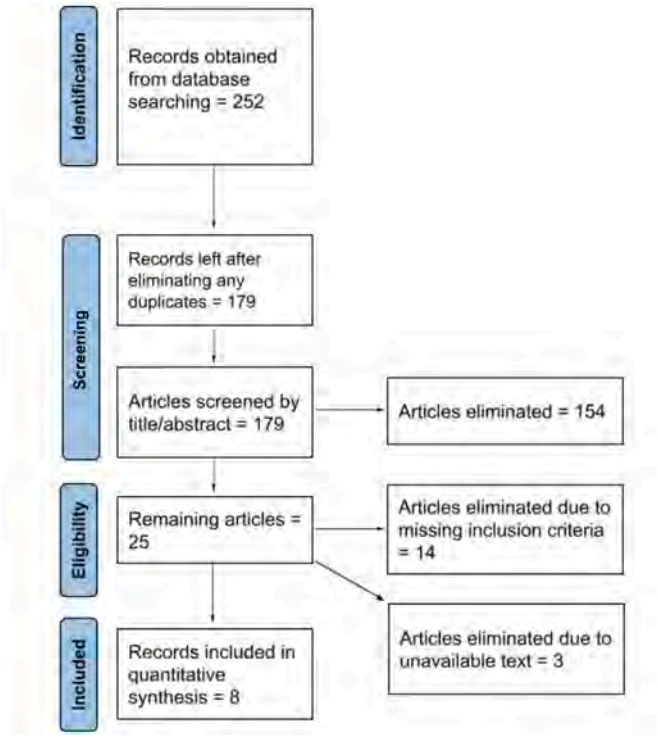

Figure 2. Search strategy PRISMA fl wchart.

Results

Eight RCTs comparing the anaesthetic efficacy of articaine and lidocaine were included.[8-15] Bias detected included failure to blind study personnel, incomplete outcome data and selective reporting (**Figure 3**). All studies examined the proportion of patients experiencing sufficient analgesia in both lidocaine and articaine groups, which was performed using electric pulp testing, pinprick test or pain during procedure. Despite consistent methodology, no EPT output or pressure on pinprick test was replicated by other studies as not all studies stated the EPT output used or the force applied when administering the pinprick test. Six studies showed that articaine successfully anaesthetised more patients than lidocaine. Whilst articaine's trend of performing better in these primary outcomes is visible, the difference in effectiveness between LAs and the number of participants used in each individual study does not correlate, making the evidence disreputable.

Other secondary outcomes were also reported, with five studies assessing pain on injection and four studies considering the time to onset of anaesthesia. Pain on injection and pain during extraction was assessed using a visual analogue scale (VAS) by asking the patients to

rank their pain on a scale of 0-100mm[8,10-12] or 0-170mm.[9,14] The onset for articaine anaesthesia is between 36 seconds to 14 minutes, whilst lidocaine becomes effective within 18 seconds to 20.5 minutes. The buccal infiltrations showed no significant difference in the amount of injection pain or onset of anaesthesia, indicating that articaine and lidocaine provide a similar level of efficacy.[8-12,14] Therefore, discomfort is unlikely to play as large a factor as primary outcomes when choosing a local anaesthetic.

	Random sequence generator (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Abdulwahab et al. (2009)	+	+	+	—	+	—	?
Evans et al. (2008)	+	+	+	—	+	?	?
Kanaa et al. (2006)	+	+	+	—	+	?	?
Kumar et al. (2019)	+	+	+	+	+	?	?
Majid et al. (2018)	+	+	+	—	+	?	?
Rayati et al. (2018)	+	+	+	—	+	?	?
Robertson et al. (2007)	+	+	+	—	+	?	?
Srinivasan et al. (2009)	+	+	+	—	+	?	?

Key

—	High risk of bias
?	Unclear risk of bias
+	Low risk of bias

Figure 3. Risk of bias table based on Cochrane risk of bias (ROBVIS).[4]

There were heterogeneous results for pain during dental extraction and electric pulp testing with six studies showing a trend of better anaesthetisation with articaine[8,10-11,13-15] and two studies showing a similar proportion of patients successfully numb from both LAs assessed.[9,12] Two results from the VAS scale for extracting posterior teeth were also shown to be heterogeneous,[11,12] however results from VAS on injecting were shown to be more homogenous in the studies reviewed.[8-10,12,14] Therefore, no conclusions could be made as to the anaesthetic efficacy in any of these studies (**Table 1**). Injections are technique sensitive, and results varied greatly between the studies. The percentage of patients receiving successful anaesthesia with articaine ranged between 25-100% and 2-86% with lidocaine. These large, overlapping data spans (mainly without p values or confidence intervals) indicate that current studies do not corroborate, and the discrepancy is too great to form an absolute conclusion on efficacy.

Discussion

> *Regardless of clear methodology, injection technique varies between practitioners and the observed studies are unlikely to be generalisable to the wider population because of this.*

Furthermore, the clinical trials in this review reported small sample sizes and therefore may not be representative and could be underpowered, particularly for secondary outcomes. The age of participants in the studies ranged from 17-65 years old. Despite this broad age range, it is impossible to assess the efficacy for that of the elderly or paediatric population from this review. A search for available literature yielded no reviews on efficacy investigated across an extreme range of ages and therefore there is need for further study on this complex subject. If studies choose to investigate the effect of age on local anaesthetic efficacy, they will likely have to consider polypharmacy, comorbidities and the porosity, density, and maturity of bone.

One study used topical anaesthetic gel with each injection. While this may reduce pain and improve patient experience, it could confound effects seen from injectable solutions alone. Dentists may consider using topical LA for patient comfort which is paramount in the GDC's standards (principle 1.2.4.). All dentists should manage patients' dental pain and anxiety appropriately. Whilst not always required for operative procedures, this individual study applying topical anaesthetic complicates the debate. The results due to the inclusion of topical anaesthetic may conflict with those of the other reviewed studies. The data from this will not give sufficient evidence towards the effect of topical LA compared to not using topical LA. The changes to VAS, efficacy, onset, or successful anaesthesia cannot be determined due to this limited evidence.

As the eight RCTs used different methods for measuring anaesthetic efficacy (e.g., electric pulp testing versus VAS), comparison between studies was difficult and could account for the huge variability in results. Two VAS scales were used which ranged from 0-100mm and 0-170mm, which makes comparisons between these scales difficult. Results depend on the patients' perception of pain and understanding of the scale, so patients' responses to the pain cannot be calibrated and are difficult to reliably compare. In contrast EPT and pinprick pressure results could be standardised by having the same output and pressure applied respectively on each patient to assess sensitivity in the pulp. Nonetheless, direct comparisons between the solutions were formed within each study. From the limited evidence available, it appears that articaine and lidocaine perform similarly for most efficacy-based outcomes, however all included studies were deemed to be at risk of bias (**Figure 3**).

Conclusion In conclusion, this review closes the gap on recent evidence and largely agrees with existing literature.

> *Insufficient evidence exists to conclusively answer the question of whether 4% articaine (1:100 000 adrenaline) or 2% lidocaine (1:100000 adrenaline) provides greater efficacy during dental treatment in posterior teeth.*

Therefore, this review cannot recommend either solution and further research is required. Ideally this would involve larger RCTs with better external validity or perhaps split mouth trials (which are unique to dentistry), where articaine and lidocaine would be randomly assigned to the right or left side of the same patient's mouth mitigating against confounding factors. Furthermore, trials should aim to use similar outcome measurements to improve the homogeneity of data for meta-analysis.

Table 1. Summary table of included publications (and results).

Study no.	Author	Country	Design	Intervention	Vol. of solutions	Purpose	Site	Population observed	Method of assessing anaesthesia	Onset of anaesthesia (mins)	No. achieving successful anaesthesia:	VAS Inject (Mean)	VAS during XLA (Mean)
1	Abdulwahab et al.[8]	USA	Randomised, doubled blinded crossover study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	0.9ml articaine/lidocaine	Pulp anaesthesia	Mandibular 1st molars	n = 18 (18 articaine/lidocaine) range of 18-53 years	EPT	14 = articaine, 8 = lidocaine (to peak anaesthesia)	7/18 = articaine, 3/18 = lidocaine	26.2mm = articaine, 27.6mm = lidocaine	
2	Evans et al.[9]	USA	Randomised, double blinded crossover study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.76ml articaine/lidocaine	Pulp anaesthesia	Maxillary 1st molars (20 left, 20 right)	n = 40 (40 articaine, 40 lidocaine) range of 18-65 years	EPT	3.3 +/- 2.35 = articaine, 3.7 +/- 2.29 = lidocaine	31/40 = articaine, 29/40 = lidocaine	44+/-29mm = articaine, 36+/-26mm = lidocaine	
3	Kanaa et al.[10]	UK	Randomised, double blinded crossover study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.8ml articaine/lidocaine	Pulp anaesthesia	Mandibular molars	n = 31 (31 articaine/lidocaine) range 20-30 years	EPT		20/31 = articaine, 12/31 = lidocaine	20.9+/-17.9mm = articaine, 17.8+/-14.9mm = lidocaine	
4	Kumar et al.[11]	India	Randomised, triple blinded parallel study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.8ml articaine/lidocaine	XLA	Maxillary 1st molars	n = 100 (50 articaine/lidocaine) range 18-60 years	Rescue injections if unanaesthetised	<5 for buccal, <5 for palatal in 44/50 = articaine, 21/50 = lidocaine	44/50 = articaine, 21/50 = lidocaine (Required no additional injections)		35.23mm = articaine, 65.77mm = lidocaine
5	Majid et al.[12]	Iraq	Randomised, double blinded parallel study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.8ml articaine, 3.6ml lidocaine	XLA	Maxillary molars	n = 84 (28 articaine/lidocaine) range of 17-60 years	Pinprick Test		24/28 = articaine, 24/28 = lidocaine	35 +/- 11mm = articaine, 36+/- 10mm = lidocaine	18 +/- 7mm = articaine, 22+/- 10mm = lidocaine
6	Rayati et al.[13]	Iran	Randomised, double blinded parallel study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.8ml articaine/lidocaine	XLA	Mandibular molars	n = 133 (72 articaine, 61 lidocaine) range of 20-60 years	Pinprick Test followed by soft tissue dissection		18/72 = articaine, 1/61 = lidocaine		
7	Robertson et al.[14]	USA	Randomised, double blinded crossover study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.76ml articaine/lidocaine	Pulp anaesthesia	Mandibular molars and premolars	n = 60 (60 articaine/lidocaine) range of 18-60 years	EPT	1st premolar 4.7 +/- 2.4, 2nd premolar 4.3 +/- 2.3, 1st molar 4.2 +/- 3.1, 2nd molar 4.6 +/- 4.0 = articaine, 1st premolar 6.1 +/- 3.1, 2nd premolar 6.9 +/- 6.6, 1st molar 7.7 +/- 4.3, 2nd molar 11.1 +/- 9.5 = lidocaine	1st premolar 49/57, 2nd premolar 55/60, 1st molar 52/60, 2nd molar 45/60 = articaine 1st premolar 35/57, 2nd premolar 40/60, 1st molar 34/60, 2nd molar 27/60 = lidocaine	36+/-30mm = articaine, 37+/-36mm = lidocaine	
8	Srinivasan et al.[15]	India	Randomised, double blinded parallel study	4% articaine, 2% lidocaine (1:100,000 adrenaline)	1.7ml articaine/lidocaine	Endodontic access	Maxillary 1st molars and premolars	n = 40 (20 articaine/lidocaine) range of 18-40 years	Pain from access cavity		1st premolar 10/10, 1st molar 10/10 = articaine, 1st premolar 8/10, 1st molar 3/10 = lidocaine		

Acknowledgements This work would not have been possible without the continued support and encouragement of Dr Mark Gormley and Dr Akhila Muthukrishnan affiliated with the University of Bristol (Bristol, UK) and the INSPIRE editorial team.

Contribution statement Rebecca Pullin and Scott Kilpatrick analysed the primary articles, composed the review, and approved the final version for publication. Both authors are guarantors of this work.

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Review

Should mindfulness-based stress reduction programmes be implemented in medical schools to foster student wellbeing?

Larai Bowers
Year 1, Medicine, University of Exeter
Email: lnb206@exeter.ac.uk

Abstract

Medical students (MS) are at a higher risk of mental illness due to the demands of their course and future profession. Mindfulness-based stress reduction (MBSR) programmes utilise mental and physical techniques to achieve self-awareness and acceptance. The evidence base for MBSR in MS is limited, however, the studies to date still shed light on the need and potential for interventions that improve mental health in MS. MBSR has a positive effect on stress, anxiety and burnout in MS but shows mixed results for empathy and depression. MBSR must be modified to suit MS' needs and can be implemented within existing elective modules to achieve satisfactory engagement. Future research should focus on MBSR in males, negative MBSR outcomes and the transferability of these skills to enhance patient care.

Abbreviations

MBSR - Mindfulness-based stress reduction
MS - Medical Students

Introduction

The pursuit of a medical career appears to come at a cost.[1] Medical students (MS) are at higher risk of suicide ideation, mental illness,[2] burnout,[3] and lower quality of life.[4,5] This population is faced with a myriad of stressors, for example, psychosocial factors, academic, and clinical factors, such as exposure to human suffering, and death.[2,4,5]

During the COVID-19 pandemic, MS have proven to be more susceptible to mental illness than their age-matched population.[5,6] Recent studies found a 61% and 70% increase in anxiety and depression respectively,[5] as well as an increase in emotional exhaustion, a contributing factor to burnout.[6] These factors arise in medical school but persist throughout their medical careers, continuing to have deleterious effects on future doctors and patient care.[3,7–10]

Mindfulness, defined as 'the intentional self-regulation of attention from moment-to-moment,[11] aims to bring about non-judgmental awareness and acceptance.[8] Mindfulness practice has been proposed to reduce stress and burnout in healthcare professionals,[12] prevent ethical erosion (a phenomenon whereby sensitivity and ethical awareness diminishes due to the negative effects of health-care training and practice),[13] and aid coping with the demands of personal and professional life.[14] Mindfulness-based stress reduction (MBSR) programmes have been investigated in clinical,[11] and non-clinical populations, including in MS.[1] Interestingly, MBSR has also been linked to changes in the brain that are responsible for emotion regulation and self-referential processing.[15] These are principles that may support the development of students into balanced professionals.

This review aims to explore MBSR-like programmes in MS and the impact these have on MS mental wellbeing or the quality of care that MS deliver. Furthermore, the feasibility of including such programmes in current medical curricula will be discussed. This will be achieved by reviewing the existing evidence of MBSR outcomes in

MS. Some studies have modified the traditional MBSR programme to better suit MS.[1] The second part of the review will explore how these modifications enhance the viability of MBSR in the medical curricula. These findings may aid in the development of a mindfulness intervention tailored specifically for MS to foster their wellbeing.

Methods

A literature search in PubMed, PsycINFO, Embase, and MEDLINE was conducted to identify studies that describe the use of MBSR for mental wellbeing in MS. The selection process is shown in **Figure 1**.

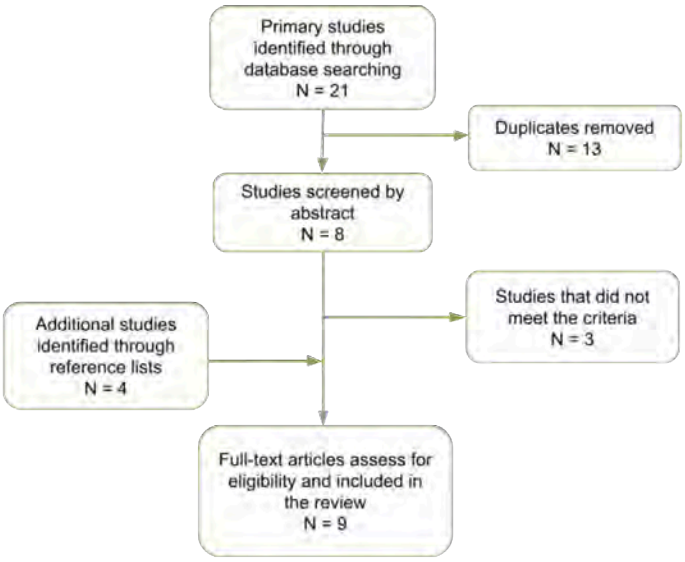

Figure 1. PRISMA fl w diagram detailing number of articles in initial search, abstracts screened and full-text articles included.

The search strategy was based on keywords: Medical student, Stress, burnout, anxiety, "mindfulness-based stress reduction" and "mindfulness-based interventions". Moreover, variations in search terms, truncation, and Boolean operators were implemented to ensure that the necessary literature was located.

Studies had to meet the inclusion criteria detailed in **Table 1**. Articles that did not include MS or describe the intervention as MBSR or modified MBSR were excluded from this review. According to the founder of the MBSR programme, Kabat-Zinn, the group discussion is a core component.[11,16] This key feature is implemented to foster mindful communication and aids in initial reflective processes.[16]

Table 1. Inclusion criteria for review.

Criteria	Description
Core components of MBSR[11]	1. Didactic teaching for stress management 2. Physical and mental exercise to increase mindfulness and promote moment-to-moment awareness 3. A group component for reflection
Outcomes (at least one)	Depression, anxiety, burnout or satisfaction
Published	In English with full text available

Discussion

MBSR outcomes in MS

Stress Stress is often considered an 'occupational hazard' in the medical profession and is an important focus for this topic[12] Awareness allows the individual to observe stress in a non-judgmental manner, reducing its effects.[8,11] This is evident in many studies reporting reduced psychological distress, perceived distress,[10,13,14,17–19] and somatisation.[13] However, follow-up times and sample sizes are often inadequate to deduce the longevity of this outcome.[10,13,17–19]

It must be noted that these improvements occurred in individuals who were not screened for evidence of clinical pathology and so may not provide evidence for students experiencing clinical symptoms, which may sometimes be the case, especially during exam periods. No confirmed physical or mental health test was given to the participants in these studies,[14] yet they were described as being in "good health".[13,14] Most studies to date rely on volunteers so any significant reduction in stress in the MBSR group must be taken with caution as students with higher distress may have been more inclined to opt for the MBSR, thus introducing bias.[13] For this reason, it is recommended that future studies administer a mental health test (e.g. a mental health screening questionnaire) before commencing the intervention to strengthen the validity of findings. Nevertheless, these combined findings are still important as they may influence students' coping ability with patient-care-related work stress.[14]

Anxiety In a study analysing mood disturbances in the face of exams, self-reported anxiety levels remained stable in students partaking in MBSR, whereas the control group reported a significant increase in anxiety.[13] These findings are supported by a pioneering study in which students partaking in MBSR demonstrated less anxiety in both the state (reaction to an event) and trait (personality feature) domains.[10] Additionally, a reduction in trait anxiety had a positive effect on state anxiety and depression,[10] which further supports MBSR's potential to foster self-awareness in individuals and reduce the impact of stressors within their personal and professional lives on their work.[13,14]

Depression Anxiety and depression were coupled in some studies.[13,18] Of the 5 studies reporting depression, three studies stated significant reductions with the use of MBSR.[10,20,21] Van Dijk *et al.*[14] reported significant improvements in mental state (anxiety and depression) with MBSR and a much larger effect size compared with the active control, somatic relaxation. Furthermore, they found increased empathy followed a reduction in anxiety and depression measures.[10] With a proposed prevalence of 40% of MS suffering from depression[22] or at increased risk of depression,[2,5,12] there should be more studies primarily measuring the effect of MBSR on depression.

Burnout prevention Burnout was not a common outcome measure used to assess the efficacy of MBSR. One study, conducted between 1996 and 2000, reported no significant difference in burnout rates between students approaching examinations who undertook a 10-week course of MBSR (n=140) and those approaching exams in the control group. However a significant increase in burnout was reported in the control group (n=162) from baseline, implying the MBSR group was more stable.[13] Furthermore, 58 4th-year students self-reported that emotional exhaustion (defined as a feeling of fatigue in the morning at the thought of going into school) had improved as a result of MBSR.[21] However, these conclusions are based upon the results of a self-reported questionnaire, thus decreasing the confidence in this result. It is hypothesised that compassion may relieve emotional tension, becoming a remedy for burnout.[8] However, contrasting findings were seen in other studies.[13,19] De vibe *et al.* concluded that the addition of MBSR did significantly reduce student burnout rates, despite identifying a non-significant reduction in burnout rates in female students.[19]

Improved quality of care A lack of self-awareness or compassion fatigue due to poor mental health can undermine humanistic care, reducing the quality of patient care.[3,8,10,14] A randomised trial found no difference in self-reported empathy in clinical settings following MBSR.[14] However, in a pilot study, 69% of students partaking in MBSR reported a positive change in their ability to deal with patient

suffering and be mindful in clinical interactions.[18] This difference may be due to MBSR improving factors other than empathy, such as communicative skills, that affect clinical performance,[8,10,12,21] or may reflect elimination of confounding variables in the randomised study. Unfortunately, studies investigating the potential for positive mindfulness skills to translate to improved quality of care remain scarce.[12]

Feasibility of MBSR in medical curricula

Acceptance A systemic problem in medical education is the lack of time for self-care.[23] Adherence to class attendance and home practise in MBSR was associated with decreased mental distress in several studies.[10,19] About 71% of students were willing to participate in an 8-week MBSR program in one study and 98% stated they would recommend the MBSR course to others.[13,14] Despite these perceived benefits, and reduced session times, students still dropped out due to "academic demands"; one study had a 20% drop-out rate.[13,14,17,20] Adherence to the recommended home practice was particularly low,[17,18] with one study finding that only 13% of students adhered.[18] Therefore, the existing demands of medical school must be considered in the development of an MS-specific MBSR.[17]

Female volunteers were dominant in most studies (53-76%).[10,14,19] One study observed significant improvements in mental distress and wellbeing in females only with an MBSR intervention, though males accounted for less than a quarter of the sample population (24%).[19] A possible explanation for sex differences may be that women report higher depression and burnout than men.[2,9] Alternatively, MBSR may help females handle their stress more than males, with males requiring a different or more extensive intervention.[19] This highlights the need for more evidence for MBSR in male MS.

Customised MBSR All studies included in this review described modified MBSR interventions, adapted to better suit MS.[14,17,19,23] Modification was necessary as longer format MBSR programs contributed to increased workload and stress causing reduced wellbeing and engagement, thus being counterproductive.[23,24] A review of 30 studies found no significant association between MBSR class hours and psychological distress variables, such as anxiety and depression;[24] however, research into class hours and the longevity of the outcomes is scarce. Understanding of the mechanisms through which MBSR brings about beneficial effects, as well as the duration of practice required to elicit beneficial outcomes remains unclear.[10,24] These uncertainties must be explored with long-term studies that assess proposed mechanisms such as rumination and self-compassion.[10,24]

The training required to facilitate MBSR is an intensive course taken over years, with a dedication to personal practice.[12] Expertise of the instructor may be a necessary requirement for optimal results from a shortened programme;[24] although not adequately described in most studies, this was probably not the case.[18,24] Despite this, in the peer-led pilot study a significant change in stress, self-compassion, and altruism was observed following MBSR;[18] however, these results may lack generalisability due to the small sample size of 30 students. Further research is necessary to deduce the feasibility of peer-led MBSR in MS, though this is a popular form of MBSR in medical education.[25]

Implementation Many studies incorporated MBSR into the existing modules within the curriculum, for example, professional development.[10,13,14,23] However, module credits or other incentives may undermine the understanding of mindfulness benefits outside of the course if students chose to participate for the wrong reasons.[10,17,19]

Qualitative analysis of attitudes of 140 MS towards extracurricular MBSR in one study revealed that such programmes would not be popular with students.[13] A further study found that the feasibility of integrating MBSR during working hours was achievable despite competing with a high workload.[14]

Compulsory or elective A study of MBSR programs running from 2013 to 2014 found significantly higher satisfaction and engagement rates and lower levels of discontentment with an optional MBSR program compared with a compulsory one.[23] It is possible that these findings are attributable to prior knowledge of MBSR from the mandatory involvement in year 1, which provided additional motivation or promoted understanding of benefits in year 2 students during the optional component.[19,23] This study suggests that offering the course on a compulsory basis and thereby eliminating the aspect of choice, may undermine the desired outcomes of mindfulness. This could be overcome by notifying prospective students before they choose to attend a medical school with obligatory MBSR.[14,23] Conversely, results of an elective MBSR programme may not penetrate the population sufficiently to address the poor mental health within MS.[26]

Limitations

The scarcity of male participant data in the literature is noteworthy as there are gender differences in emotion experience and expression and therefore MBSR may not have assisted males in handling stress.[19] This was highlighted in a study where MBSR only elicited a positive outcome in female participants.[19] It must also be noted that there is a significant lack of published research on the negative outcomes of MBSR.[12] The lack of data for males and potential publication bias mentioned may result in a misconceived idea that MBSR is beneficial for everyone.[10,14,19,27]

Additionally, despite higher rates of mental illness in MS, the literature addressing MBSR in clinical mental illness is scarce, thus imposing a significant challenge to extrapolate the evidence to address clinical anxiety or depression. If the course was to be offered as a core component of the curriculum, these issues must be addressed first to ensure safety.[23]

Conclusion

There is evidence to support the role of MBSR in stress reduction and prevention of burnout and anxiety, however, mixed results have been reported with respect to depression and empathy. Long-term studies across a diverse MS population, including students with clinical mental illness, should be conducted to provide stronger evidence of MBSR effectivity. Future studies assessing the influence of MBSR on humanistic care may also support preliminary research that suggests MBSR can improve the quality of patient care.

MBSR appears to be largely accepted as a method to improve subclinical mental wellbeing in MS. This, however, is subject to the programme being integrated optionally, into the existing curriculum. Due to the scarcity of research in this area, particularly with respect to male students or the negative effects of MBSR, implementation on a compulsory basis cannot be confidently promoted based on current evidence. Further research into the outcomes of an elective modified MBSR programme, factoring the stressors in medical education with a trained facilitator, would make a valuable contribution to the field and to addressing mental health challenges in MS.

Acknowledgements I would like to express my gratitude to my facilitator, to Dr Raluca Topciu, Senior Lecturer in Clinical Research (University of Exeter, Exeter, UK), for guiding me through my student specific study unit and inspiring me to share my findings.

Contribution statement The author has made substantial contributions to the conception or design of the work, drafting the work and has given final approval of the version to be included in Inspire.

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Review

To what extent does education disparity affect the prevalence of female genital mutilation in Sudan?

Kamal El-Badawi
Year 4, Medicine, University of Plymouth
Email: kamal.el-badawi@students.plymouth.ac.uk

Abstract

Female genital mutilation (FGM) is the act of partially or totally removing the external female genitalia for non-medical reasons. This work aimed to define and provide an overview of FGM, summarise the prevalence, identify some key reasons as to why it is practiced and explore the methods that can be utilised to correct education disparities amongst the population. A review of the literature was conducted using systematic searches of the PubMed database and of the United Nations International Children's Emergency Fund (UNICEF) website, with supplementary Google searches to obtain information regarding the Saleema Initiative. The Saleema Initiative, set up by UNICEF, aims to change the attitudes of Sudanese society and ultimately reduce the prevalence of FGM by introducing community pledges against FGM and dispelling myths regarding the practice. Available data demonstrates that the higher a person's level of education, the less likely they are to support or carry out FGM. However, it remains unclear as to what extent education influences the prevalence of FGM within populations. Sexual and reproductive health education and comprehensive sexual education both have positive impacts on perceptions of FGM. Recent re-criminalisation of the practice in Sudan may also reduce prevalence; however implementation must be firmer than with previous legislations.

Abbreviations

CSE - Comprehensive sexual education
FGM - Female genital mutilation
FGM/C - Female genital mutilation/cutting
MICS - Multiple indicator cluster surveys
NCCW - National Council of Child Welfare
PTSD - Post traumatic stress disorder
SRHE - Sexual and reproductive health education
UNFPA - United Nations Population Fund
UNICEF - United Nations International Children's Emergency Fund
WHO - World Health Organization

Introduction

Female genital mutilation (FGM) is defined by the World Health Organization (WHO) as "all procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for non-medical reasons".[1] It is one of the most detrimental non-medical procedures carried out in the modern day, and causes significant harm to individuals, as well as lifelong physical and psychological complications. The practice is very controversial across the world and is seen as a human rights violation by many. However, it is still carried out in some areas of the world, largely in Africa.[2]

The different types of FGM are:

- Type I: clitoridectomy - the partial or total removal of the clitoris
- Type II: excision - the partial or total removal of the clitoris and labia minora
- Type III: infibulation - the narrowing of the vaginal opening through the creation of a covering seal.[3]

> *The practice is dangerous and is usually carried out by a traditional practitioner using unsterile equipment and without sedation.[4]*

As a result of the procedure, there are significant short- and long-term issues. Short-term sequalae which have been reported include bleeding, shock, infection, problems with urination and wound healing.[5] Long-term sequalae include recurrent genitourinary infections, painful sex, obstetric complications (e.g. tears, lacerations, intrapartum death and post-partum haemorrhage), and mental health disorders, which are commonly overlooked, including post-traumatic stress disorder (PTSD), anxiety and depression.[5,6]

In Sudan, a total of 12.1 million girls and women have been subject to FGM.[1] Sudan also has the 4th highest prevalence of FGM in the world, with the rate amongst 15-49 year olds being 86.6%.[7] FGM is deeply rooted within Sudanese culture and tradition and it is still justified by some as a religious practice. The Sudanese government and international organisations have attempted various interventions to decrease the rates of FGM in Sudan. Unfortunately, most of these have been unsuccessful, prompting the need for a different approach.[1]

Within the Sudanese community, information regarding the practice comes primarily from family and friends, resulting in skewed knowledge regarding the harmful effects of FGM.[8] This, combined with the lack of teaching in schools on the matter allows misinformation to spread easily to the next generation, preventing any positive change in people's lives. In-school education by teachers and out-of-school teaching by the Saleema Initiative could be used to influence society. Specifically, the Saleema Initiative strives to start discussion around the practice and prompt changes; this is discussed in more detail below.

On the 22nd of April 2020, the Sovereignty Council of Sudan (the provisional government created after the Sudanese revolutions) recriminalised FGM and instated 3 years imprisonment or monetary fines as penalties for it.[6] However, Sudan has a poor history of implementing FGM laws and so enforcing such sanctions may be difficult.[4]

Prevalence

The prevalence of the different types of FGM varies throughout Sudan, with most sufferers having type III carried out.[9] 77.0% of those circumcised have had their genital area sewed closed.[1] The prevalence of infibulation varies greatly by state, from 36.7% in Central Darfur to 94.6% in Sinnar.[1]

Sudan was the first country in Africa to legislate against FGM. Infibulation was made illegal in 1946 after an amendment to the Penal Code.[5] However, under this code, type I and type II FGM were still permitted and in some areas legislation was not enforced.[5] A further amendment to the code in 1991 did not mention FGM ruling and so, until its recriminalisation in 2020, there were no laws against the practice. Despite this, the rate of infibulation in Sudan has decreased from 81.9% in 1980 to 72.1% in 2014.[2] This shows signs of a shift in societal attitudes against the practice; however, there is still a lot of work left to be done.

According to the Human Rights Watch, the following are reasons for people practicing FGM:

- Societal pressures: there is pressure to conform with those around you, otherwise you face being rejected by your family.
- Hygiene and aesthetic reasons: some women think that FGM makes a girl more attractive and appealing.
- Rooted in tradition: as something that has occurred for decades, girls know that if they question or don't uphold the tradition, they will face stigmatisation and familial rejection. Therefore, girls feel as if they must preserve their cultural identity by undergoing the practice.[6]

> *The lack of knowledge regarding the harmful effects means that girls are unable to oppose those who carry out the practice on them.*

They know no better and, therefore, are subject to this inhumane act. One way of combatting this is by utilising various forms of education.

Education and FGM

Generally, there is a low societal awareness of the importance of education within Sudan.[10] The Sudanese education system has suffered greatly due to chronic resource and monetary insufficiency and both of these factors have contributed to low school attendance rates. Despite government policy mandating that primary and secondary education is free, some schools still charge tuition fees, thereby denying the poorest children access to school. Therefore, these children miss out on the opportunity to have a foothold in society.

An in-depth analysis conducted on behalf of the Sudan Free of FGC programme, a joint programme between UNICEF, the United Nations Population Fund (UNFPA) and WHO Sudan, found that the higher the level of one's education, the less likely they are to practice FGM and the less likely they are to support the practice.[1,2] Additionally, it was found that the lower the level of education, the less aware one is of the practice.[2] For example, if a mother has undertaken no formal education, their daughter has a 33.6% chance of undergoing FGM. This is compared with a 15.2% chance of FGM in daughters whose mothers have completed higher education.[2] This shows a positive impact between a mother's level of education and FGM prevalence. Education rates vary across Sudan, the national average of primary school age children out of school is 29.8%, ranging from 46.8% to 7.9% in the Blue Nile and Northern states, respectively; this figure decreases to 23.4% in secondary school age children.[11] The disparity in education between states could be due to factors including ease of accessibility, familial pressure or different life aspirations. For example, those from the Northern state have low non-attendance rates, with parents pushing their children to gain qualifications, better their lives and leave the country.[12]

This review aimed to define and give an overview of the practice of FGM, summarise prevalence statistics, identify some of the key reasons why it is practiced and explore methods of education that can be used to make positive changes in society.

Literature search

A search strategy was employed using the PubMed and Primo electronic databases. Search terms are detailed in **Table 1**. All literature analysing statistics is dated from the year 2000 onwards, as this was when the first multiple cluster indicator survey (MICS) was conducted, providing the bases for subsequent statistical reports. Prior to this, there had not been systematic data collection, resulting in fragmented data. Exclusion criteria were used to filter out resources which referenced Nigeria, due to it not being the focus of the review. As can be seen in **Table 1**, few retrieved articles referred to the Saleema Initiative. Therefore, the organisation was contacted directly to request further information and resources. Other resources were obtained from verified contacts who work for the WHO and Saleema organisations in Sudan. UNICEF and UNFPA provided information regarding Saleema. The news article that was used from the Guardian was cross referenced with a government resource.

Sexual and reproductive health education

A recent study determined that sexual and reproductive health education (SRHE) at secondary school level, with a focus on FGM and its complications, has been linked to students thinking more negatively about the practice. Post-SRHE, the percentages of students who considered FGM a human rights violation, would actively discourage FGM and support legislation against the practice increased by 14.7%, 12.7% and 13.5%, respectively.[3] Additionally, the percentage of students who supported the discontinuation of the practice increased by 11.6%, with 79% of students saying they wouldn't circumcise their daughters.[13] This example shows that

school-based SRHE has a positive impact on the attitudes of students, allowing them to understand the practice fully and empowering them to change their future for the better. To decrease the prevalence of FGM nationwide, the findings of this research must be implemented into Sudanese society via the curricula of secondary schools and SRHE should be carried out by competent teachers. Unfortunately, the stigma sex and FGM carry prevents in-school SRHE, with some preaching that sex is a sin and that talking about it is prohibited.[14] When SRHE sessions are present, they are skipped by teachers who feel uncomfortable or not adept enough to talk on the matter.[15] There is no mention of FGM or SRHE within the curriculum, showing the disregard of the importance of such matters.

Table 1. The details of the literature review process.

Search term	Filter	Items found	
		PubMed	Primo
FGM in Sudan	None	37	462
	AND education	14	322
	AND education NOT sexually transmitted diseases	13	299
	AND education AND Saleema	1	5
FGM prevalence in Sudan	None	156	289
	NOT Nigeria	72	136
	AND effect of education	82	128
	AND effect of secondary school education	45	50
	AND effect of education AND Saleema Initiative	2	3

Through initial searches, 944 articles were retrieved. After applying exclusion criteria, a total of 106 articles remained. The relevance of each article was determined, and 10 articles were finally included for qualitative analysis.

Comprehensive sexual education

An in-school method of FGM awareness known as comprehensive sexual education (CSE) equips young people with knowledge, skills and attitudes needed to enjoy their sexuality, both physically and emotionally.[16] CSE supports the basic right of adolescents to learn about their bodies, contraceptives, consent, FGM and early marriages, all of which are prevalent and taboo issues in Sudan, which are unlikely to be taught adequately by family or schools. Opening students' eyes to these matters empowers them, giving them confidence in objecting against societal wrongs like FGM.

> *However, to sustain behavioural changes, CSE must be implemented on a long-term basis, by willing and knowledgeable teachers.*[17]

Saleema

The Saleema Initiative, set up by UNICEF and the National Council of Child Welfare (NCCW) in Sudan provides communication tools that invoke discussion between members of the community resulting in changes in social norms, attitudes, and intentions relating to FGM.[18] Instead of discrediting a long-held tradition, the initiative aims to allow new social norms to displace the old ones, instilling a new threshold concept into society. Saleema translates to being "whole, healthy in body and mind, unharmed, intact, pristine, and untouched, in a God-given condition".[19] Those using the word Saleema to describe uncircumcised girls are six times more likely to reject FGM than those using other terms.[1]

The campaign runs sessions with 263 groups across Sudan, with 4 main activities:

- Sufara Saleema Campaign: publicly denouncing FGM
- Saleema Colours Campaign: wearing Saleema colours (mainly orange, red, yellow and green) as a sign of support[20]
- Community dialogue: dialogue amongst communities regarding FGM, its role in society and its need for abandonment
- Born Saleema Project: pledging to not cut new-born daughters.[18]

This approach has shown promise and could be even more effective given the £15m investment provided by the UK government in 2018 to expand the initiative.

A study on the Saleema Initiative's efficacy involved analysing the receptiveness of the campaign amongst those in the 18 states who had been exposed to it.[19] Participants' views were recorded pre-intervention, and twice post-intervention, with the findings summarised in **Table 2**.[18] The study found changes in attitudes regarding cutting within the community, amongst friends and within Sudanese society.[18] One case demonstrated that the Saleema campaign directly affected FGM prevalence, with a village in West Kordofan rejecting the practice entirely and petitioning to change its name to "Saleema".[21] These findings point towards attitude changes caused by the Saleema campaign which has been more effective in FGM abandonment than any intervention or activism in the last 30 years.[21]

Table 2. Attitude changes towards FGM pre and post Saleema exposure.

Overall agreement by wave	Most people in your community practice FGM	Most of my friends practice FGM	It is appropriate for families in my community to practice FGM	Sudanese society in general considers it appropriate to practice FGM
Wave 1 (December 2015): pre-intervention	65.9%	58%	35%	62.9%
Wave 2 (December 2016): post-intervention	56.4%	47.6%	24.3%	48.4%
Wave 3 (December 2017): post-intervention	48.5%	41.9%	26%	44.8%
Total	58.5%	49.2%	28.4%	51.9%

Note, there was a decrease in raw values post vs pre exposure but the differences were not statistically assessed. Table adapted from Evans *et al* (2019).[18]

Conclusion

The lack of studies that specifically assess the implementation and impact of the Saleema Initiative prevents an analysis of its efficacy over time. There were only two studies focussing on the Saleema Initiative and three on CSE, so more research must be done to assess the long-term efficacy of both of these interventions.

A strength of this study is that data regarding prevalence of practice and education rates was cross referenced with similar studies, strengthening the reliability of these results.

Sudan's vast education disparity and discouragement of girls attending school are contributing factors in the prevention of societal progression and changes in attitude regarding FGM. However, the true extent to which Sudan's FGM prevalence has been influenced by the country's education disparity cannot be accurately measured.

In-school methods of teaching FGM awareness, SRHE and CSE to secondary school students have led to positive changes in attitudes. If implemented across the country using the curriculum as a vehicle, such measures could have a major impact on FGM prevalence. These methods, alongside funding and patience, could pave the way for societal changes that will better the lives of millions in the future.

Studies have shown that the work of the Saleema Initiative impacts FGM abandonment by bypassing educational disparities amongst the population and positively influencing people's views.

Cultural and religious beliefs heavily influence attitude towards the practice. For example, some individuals may not be informed of teachings of their religion yet are also told not to question traditions. Therefore, such matters must be approached with great sensitivity as to not cause offence.

The recent progressive political change, including recriminalisation of FGM in Sudan, gives hope to the people of Sudan and to health organisations that positive change will occur. More studies are needed to assess the impact of legislation changes in Sudan on FGM rates.

Contribution statement The author declares that they designed and drafted the work. The author gave final approval of the article to be included by Inspire.

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Review

What barriers do men who have sex with men face for using pre-exposure prophylaxis for HIV? A comparative study between high-, and low- and middle-income countries

Christopher Rainforth
Year 2, Medicine, University of Bristol
Email: cr15648@bristol.ac.uk

Abstract

In this review the needs and barriers of men who have sex with men (MSM) for pre-exposure prophylaxis (PrEP) implementation in high-income countries (HIC) and low- and middle-income countries (LMIC) are compared. In April 2018 and June 2021, electronic literature searches of Ovid Medline, Embase, AMED, PsychINFO and Cochrane databases were conducted. Studies were screened based on their title and abstract for relevancy, excluding papers that did not focus on MSM, PrEP and human immunodeficiency virus (HIV). Relevant studies were analysed in full, extracting and comparing applicable data. In 2018, 517 studies were identified. Of these, 207 were removed as they were ineligible or duplicates. Of the 310 eligible studies, 72 studies were analysed. It was found that adherence of PrEP must remain high for it to be effective and cost-effective. PrEP is cost-effective and sometimes cost-saving in HICs but the high cost of PrEP, owing to its patent, makes it unfeasible in many LMIC. For maximum effect on the HIV epidemic among MSM, PrEP must be used in conjunction with current HIV prevention methods, which also must be scaled-up. Previous research indicated that awareness of PrEP was low in LMIC, at 29.7%, but willingness to use PrEP was high in these countries, at 64.4%, whilst it was lower in HIC. Stigma and cost were the two greatest barriers to PrEP implementation at individual and government levels in LMIC and HIC. The worldwide rising incidence of HIV among MSM worldwide requires further prevention interventions, such as PrEP in combination with current methods. However, there are many individual- and government-level barriers to its implementation, namely stigma and cost.

Abbreviations

ARV - Anti-retroviral
HIC - High-income countries
HIV - Human immunodeficiency virus
LGBTQ+ - Lesbian, gay, bisexual, transgender, queer
LMIC - Low- and middle-income countries
MSM - Men who have sex with men
PrEP - Pre-exposure prophylaxis
QALY – Quality-adjusted life year
RCT - Randomised controlled trial
STI - Sexually transmitted infection
TDF-FTC - Tenofovir/emtricitabine
UNAIDS - Joint United Nations Programme on HIV and AIDS
WHO - World Health Organization

Introduction

Despite reductions in incidence of human immunodeficiency virus (HIV) among many heterosexual populations worldwide, men who have sex with men (MSM) are disproportionately affected by HIV.[1] There is a high prevalence of HIV among MSM, averaging 15% worldwide but reaching as high as 25.4% in the Caribbean,[1] which is significantly higher than the general adult HIV prevalence of 1% in the Caribbean.[2] Prevalence is continuing to expand in most countries among MSM as incidence rates of HIV remain at the same level or increase, particularly in low- and middle-income countries (LMIC).[3]

MSM are on average 24 times more likely to acquire HIV than the general population,[4] in part due to the 18 times higher per-act risk of unprotected receptive anal intercourse than unprotected vaginal intercourse.[1]

To combat the disproportionate burden of HIV in MSM worldwide the World Health Organization (WHO) recommend a combination of prevention interventions, including testing, counselling, condoms, early anti-retroviral (ARV) treatment and pre-exposure prophylaxis (PrEP).[5] Consistent condom usage has been declining in high-income countries (HIC)[6] and LMIC[7,8] and HIV testing is significantly easier in HIC[9] than in LMIC.[10] Therefore, to halt and reverse the expanding HIV epidemic among MSM1, the WHO strongly recommend PrEP.[11]

PrEP is a relatively new HIV prevention method that uses ARV drugs to protect people from acquiring HIV.[12] High adherence before and after exposure is required for it to be efficacious.[13] PrEP is mostly taken as a combination of the ARV drugs, emtricitabine and tenofovir disoproxil fumarate.[12]

The effectiveness of PrEP in preventing HIV acquisition has been determined by 10 studies, 3 of which involved MSM.[12] These three studies found PrEP to be highly effective if adhered to properly, with relative risk reductions of HIV acquisition of 95% (95% CI 70-99%; p<0.001),[13] 86% (95% CI 40-98%; p=0.002)[14] and 86% (90%CI 64-96%).[15] Before PrEP can be fully implemented for MSM, the barriers must be understood.

This review used the World Bank definitions of HIC and LMIC, where HIC had a gross national income per capita of greater than $12,536 in 2019.[16] A systematic literature review was conducted to identify the needs and barriers of MSM accessing and using PrEP to prevent acquisition of HIV. It compares the individual-, structural- and government-level needs and barriers to MSM for using PrEP between HIC and LMIC. Themes identified included awareness of PrEP, willingness to use it, associated healthcare costs, stigma and criminalisation of homosexuality.

Literature search

In April 2018, an initial library search was conducted using Cochrane library and Ovid (Ovid Medline, AMED, PsycINFO and Embase) databases to identify literature that analysed PrEP for HIV among MSM. The search used the keywords "PrEP", "HIV", "MSM" and their variations and then combined the results using "AND". Medical Subject Heading terms were used with 'explode' to ensure all term variations were covered.

2018 literature search

Ovid search The search terms used with Ovid and the articles found are displayed in **Table 1**. All papers found by search number 15 (n=488) were exported to Endnote, where any duplicates were removed (n=14), leaving 474 articles.

Table 1. Search terms and findings f om 2018 Ovid search.

Search number	Search term	Number of articles
1	pre-exposure prophylaxis or preexposure prophylaxis or "PrEP" or HIV pre-exposure prophylaxis or HIV preexposure prophylaxis or pre-exposure antiretroviral prophylaxis or preexposure antiretroviral prophylaxis or pre-exposure chemoprophylaxis or preexposure chemoprophylaxis or anti-HIV prophylaxis	4436
2	MeSH: Pre-Exposure Prophylaxis - explode	1015
3	1 OR 2	4436
4	men who have sex with men or MSM or gay or bisexual or homosexual*	39346
5	MeSH: Homosexuality, Male – explode	13147
6	4 OR 5	39346
7	human immunodeficiency virus or HIV or acquired immunodeficiency syndrome or AIDS	423134
8	MeSH: HIV OR HIV-1 OR HIV-2 – explode	91941
9	7 OR 8	423134
10	3 AND 6 AND 9	726
11	10 limited to English language	716
12	11 limited to years 2010-Current	707
13	10 limited to Humans	552
14	12 AND 13	492
15	14 and 'Journal Article' [Publication Type]	488

Cochrane library The MeSH search terms used on Cochrane using 'explode' and the articles found are displayed in **Table 2**. All articles found by search number 4 (n=29) were also exported to Endnote, where duplicates were removed (n=26), leaving 3 articles.

Table 2. Search terms and findings f om 2018 Cochrane library search.

Search number	Search term	Number of articles
1	Homosexuality, male	331
2	Pre-Exposure Prophylaxis	96
3	HIV	3059
4	1 AND 2 AND 3	29

Analysis The combined articles found by the 2018 searches (n=477) were assessed for eligibility by reading the title and abstract.

Exclusion criteria Studies focussing on non-MSM populations or non-PrEP HIV prevention methods were excluded, as were letters, commentaries, inaccessible papers and studies published before 2012, unless the study was a randomised controlled trial (RCT) assessing PrEP effectiveness (n=1). A total of 167 studies were excluded, leaving 310 eligible studies (see **Figure 1** for flow diagram of search).

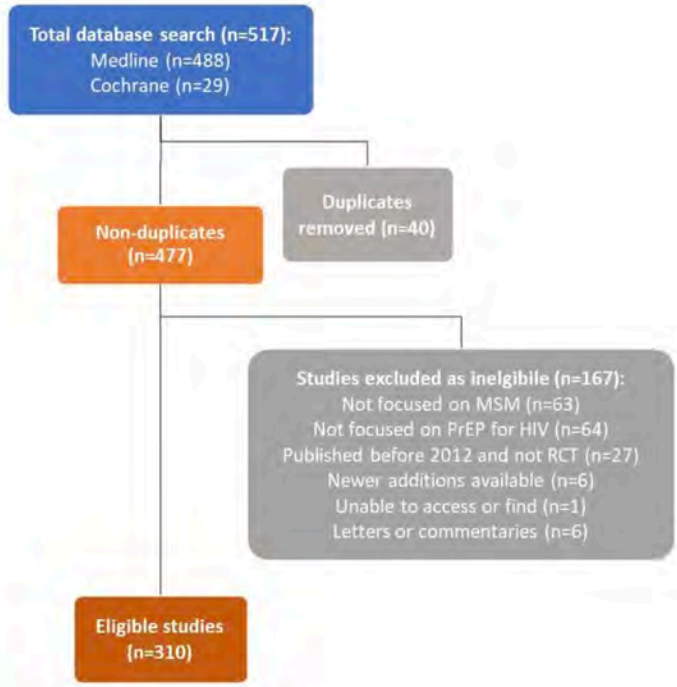


Figure 1. Flow diagram of 2018 library searches

Inclusion criteria Papers published in 2015-2018 (n=218) were initially prioritised for analysis as they were the most recent, giving up-to-date information at the time of the study. They were grouped by geographical region when mentioned in the paper's title or abstract (n=134; **Table 3**), leaving 84 papers that did not have any mention of geographical region.

Table 3. Number of articles per geographical region from 2018 search.

Region	Studies identified as country-specific from title or abstract	Most relevant studies taken as a sample from each region	Studies fully analysed from each region
Africa	7	7	5
Asia	1	9	8
Australia	4	2	2
Canada	6	1	1
Europe	20	15	11
Latin America	6	4	3
Multi region	20	15	15
USA	54	26	11
Total	134	79	56

Meta-analyses and multi-region studies were prioritised to give a better global perspective, cover a greater total geographical distribution and read summaries of many of the other papers found. Due to the far greater number of papers in North America and Europe, only a sample of papers from these regions were analysed and read in full, whereas most studies in LMIC were fully analysed (see **Table 3**). Studies published in 2012-2014 were then screened for themes not covered in the 2015-2018 publications.

WHO and Joint United Nations Programme on HIV and AIDS Further to the library literature searches, the WHO and Joint United Nations Programme on HIV and AIDS (UNAIDS) websites were searched for publications and guidelines for PrEP in MSM to prevent HIV. There were 3 relevant publications from the WHO website and 4 from the UNAIDS website, which were analysed for relevant ideas.

In total 76 publications were analysed in full, with 56 being discussed in this paper (see **Figure 2**). Publications that were analysed and not discussed extended beyond the scope of this review or lacked relevance to the review question.

2021 library search

An update of this review was conducted in June 2021 via an additional library search, using the same methodology as the 2018 search. This resulted in 929 potentially applicable articles from 2018-2021 being found. The same inclusion and exclusion criteria as in the 2018 search yielded 444 eligible publications, of which systematic reviews (n=20) were fully analysed to extract new themes and to reinforce previous ideas; four of these articles were included in this review.

Awareness of PrEP

Six studies in LMIC assessed the awareness of PrEP among MSM. One meta-analysis analysed 23 articles and found awareness of PrEP to be low in LMIC at 29.7% (95% CI 16.9%-44.3%).[3] However, awareness was higher in a few studies (61.3%-72.8% in Brazil, Thailand and China).[17-20] Higher awareness was associated with older age, greater education levels, employment[17-21], and receiving a sexually transmitted infection (STI) diagnosis in the previous 12 months.[17-20]

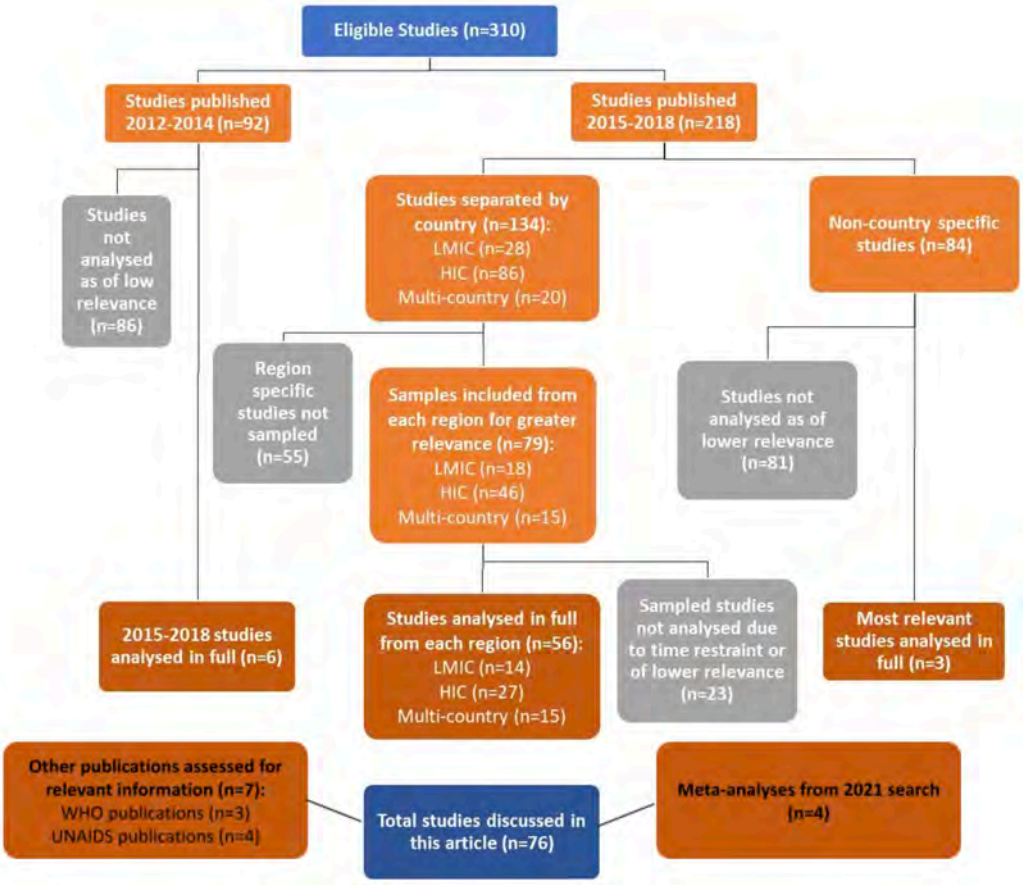
Seven studies assessed the awareness of PrEP among MSM in HIC, which was generally higher than in LMIC. One US study found that 86% of MSM were aware of PrEP.[22] However, low awareness was found in Canada (20.9%)[23] and Spain (28.7%).[24]

Willingness to use PrEP

Nine studies mentioned the willingness of MSM to use PrEP in LMIC. A meta-analysis of 20 studies in LMIC showed high hypothetical willingness to use PrEP once participants were made aware of it, at 64.4% (95% CI 53.3%-74.8%).[3] Higher self-perceived risk of HIV acquisition and engaging in higher risk activities (including increased number of partners and sex with HIV-positive partners) were found to have a positive association with being willing to use PrEP.[7,25-28] Older MSM were more likely to be willing to use PrEP in China,[19,29] whereas some studies reported willingness to use PrEP was higher among MSM with lower income.[30]

Six studies discussed willingness to use PrEP in HIC, which was generally lower than in LMIC.[31] High willingness to use PrEP was found in Spain (57.6%)[24] and in[20] American cities (61%).[32] Moreover, in an open-label US study, 60.5% of eligible participants joined the tenofovir/emtricitabine (TDF-FTC) arm of the study.[33] Willingness to use PrEP was lower in the Netherlands (only 13% had high intention to use),[34] Australia (31.7%)[35] and Hong Kong (7.7% were willing to use PrEP if they had to pay, whilst 45.2% it if it was free).[36] A meta-analysis found overall acceptability of PrEP to be 57.8% and to not differ greatly between developing and developed countries; instead, acceptability of PrEP was found to depend on an individual's understanding of PrEP's high effectiveness and cost.[27]

Figure 2. Flow diagram of 2012-2018 study selection for this article



Cost of PrEP

Four studies in the USA and 1 in Canada demonstrated the cost of PrEP ranged from being cost saving to costing 298,000 US dollars per quality-adjusted life year (QALY) gained,[37-41] depending on the effectiveness of PrEP.[42] PrEP was also found to be cost-effective in the Netherlands[34] and France.[43] Maximum financial benefit was found when PrEP was used in conjunction with other HIV prevention programmes.[44] Conversely, in Australia PrEP was not cost-effective at a population level,[45] and the cost of PrEP initially prevented widescale implementation in England and Wales,[43] though it is now available free of charge, on the NHS, for high-risk individuals.[46]

PrEP would be cost-effective in Peru,[47] however, the total cost of PrEP has been prohibitive to its implementation. Generic PrEP may be too expensive for large-scale implementation in Myanmar, where the HIV prevention budget is very low.[8]

Stigma and criminalisation

Removal of stigmatising barriers is essential for effective PrEP uptake.[1] Criminalisation of same-sex activity was identified in 6 studies, all of which are LMIC: Myanmar,[8] Kenya,[48] Malaysia,[29,49] Senegal[50] and Nigeria.[31]

Seven studies discussed stigma being a significant barrier to PrEP in HIC, listing homophobia, lack of 'outness' and service provider discrimination as being factors in reducing access to HIV and PrEP services.[25-28,31,51] The USA population were found to particularly suffer from stigmatising barriers due to greater community prejudices that meant that PrEP was viewed as only being 'used by whores' and promoted unsafe sex.[25-28,51] This stigma was perpetuated by healthcare professionals, who were condescending, dismissive or lacking in lesbian, gay, bisexual, transgender, queer (LGBTQ+)-specific knowledge.[25-28]

Individual barriers

Current prevention methods are failing to contain the rising HIV epidemic among MSM. Therefore, there is a need for further intervention, such as the addition of PrEP.[1,5,11] Significant barriers exist to PrEP implementation worldwide at individual and government level, including stigmatisation of HIV and sexual orientation, cost to individuals and governments, low awareness of PrEP, and the requirement of high willingness to maintain adherence.

Utilisation of an intervention requires the prerequisites of awareness of the intervention, willingness to use it and sufficient adherence.[3] Therefore, low awareness of PrEP among MSM in LMIC (29.7%) presents a significant barrier to PrEP's implementation and demonstrates an international inequality, acting as a greater barrier to implementation in LMIC than HIC.[3]

Conversely willingness to use PrEP is higher in LMIC (64.4%) than HIC,[3] which could be due to larger inadequacy of HIV services in LMIC compared to HIC.[31] MSM who engage in high-risk sexual behaviours and have higher risk perception are more likely to be willing to use PrEP for greater protection from HIV in both HIC and LMIC.[7,8,25-28] However, there is poor accuracy of predicting actual uptake based on willingness. For example, in the USA, 58% of participants expressed willingness to use PrEP but uptake was only 15%.[26,32] A range of individual circumstances and the way in which PrEP is provided may affect actual uptake,[3] including perceived or experienced side effects.[26] Further research is required to examine the broken link between hypothetical willingness, actual uptake and maintained adherence.[26]

Low willingness to use PrEP presents a considerable barrier to its uptake and adherence; stigma and cost are the primary barriers to willingness to use PrEP in both LMIC and HIC.[3] Perception of or the actual cost of PrEP reduces willingness for its use among MSM and discriminates against those who are unable to pay, creating inequality and reducing the overall effectiveness of PrEP.[25-28,52] Stigma provides barriers at individual, community, healthcare and structural levels.[25-28] High-risk sexual activity, such as unprotected sex, can lead to internalised stigma.[25-28] Fear of peers and family assuming the user is gay,[25] HIV+,[7,25] promiscuous,[25,28,29,49] engaging in high-risk sexual activity, careless about STIs or being labelled a 'Truvada whore' also

reduces willingness to use PrEP.[25-28] PrEP providers can perpetuate stigma with patronising and disdainful remarks regarding 'condomless sex' or perceived promiscuity.[25-28] Community-level stigma provided barriers in 5 LMIC[7,8] but in only 1 HIC (the USA).[53] Wider reduction of homophobia and condemnation of sexual promiscuity are required to reduce the anticipated and received stigma for PrEP users.

Structural barriers

The cost of PrEP proves to be significantly prohibitive to its implementation worldwide for high-risk populations through health policy. However, PrEP can be cost-effective/saving in America,[37, 41,42,54] the Netherlands[34] and the UK.[46] Studies that found PrEP to lack cost-effectiveness failed to account for reduced onward transmission[40] or did not prioritise key populations, reducing their real-world relevance.[39] However, proven cost-effectiveness and availability of funds in HIC demonstrate there are other factors at government-level that contribute to the lack of PrEP implementation. Even generic PrEP, which costs 1 US dollar per month, may not be financially feasible in Myanmar due to the low budget for prevention interventions.[8] The price of PrEP must be reduced for viability of implementation in LMIC and HIC.

Criminalisation of same-sex activity, as found in 6 of the included LMIC,[8] prevents governments from targeting healthcare interventions for MSM and further fuels individual-, structural- and community-level stigma, hindering access to HIV services.[1] These countries lack dedicated policies to prevent HIV among MSM generally, let alone expensive PrEP.[1] Despite a lack of criminalisation of same-sex activity, structural-level stigma also persists as a considerable barrier to HIV prevention and PrEP uptake in HIC, thus stigma is exceptionally damaging to HIV prevention efforts worldwide.

Clinical relevance and recommendations

Current HIV prevention methods, such as consistent condom usage, must be scaled-up to reverse the growing HIV epidemic among MSM. PrEP has shown to be effective when used in conjunction with other prevention methods.[55] PrEP contributed to the 32% fall in HIV diagnoses among MSM at 5 London clinics in 2015-2016 (p=0.014), with diagnoses among heterosexuals remaining constant.[55] Education of PrEP must also be used to improve the awareness of and willingness to use PrEP among MSM, helping to reduce stigma, particularly in LMIC. The high cost of PrEP may be overcome through generic manufacturing in Europe once the patent expires, and through compassionate trade deals in LMIC, which may serve to improve political will to implement PrEP. Furthermore, same-sex activity must be decriminalised or else the stigmatisation and marginalisation that drives the HIV epidemic will continue among MSM. However, such significant legal changes require considerable cultural shifts.

Strengths and limitations

The findings of this literature review build upon the myriad of studies available relating to PrEP for HIV among MSM. A unique asset of this review is the comparison of HIC and LMIC in the needs and barriers of PrEP among MSM, while most previous reviews have focused on effectiveness, willingness to use and awareness.

Time restraints and word limits prevented analysis of all relevant papers, in particular those found by the literature search in 2021, meaning themes may have been missed. The majority of studies were published in the USA and there were many more studies in HIC than LMIC. Moreover, none of the studies focussed on MSM in the Middle East or Caribbean. The greater concentration of studies in HIC and the requirement to sample papers may add unintentional selection bias to this review. Differences between MSM populations within the same country may be underreported, but this is outside of the scope of the review.

Conclusions

PrEP represents an additional preventative intervention against HIV and has been shown to reduce the incidence of HIV among MSM.[55,56] However, there are many barriers to implementation of PrEP for MSM. Primarily, societal and governmental stigma presents the greatest barrier by preventing willingness to use PrEP,[1,3] driven by criminalisation of same-sex activity,[31] and interpersonal and medical perceptions.[25-28,31] Low awareness among many individuals in LMIC inhibits MSM from accessing PrEP, but the high willingness to use among the same cohort demonstrates a requirement of PrEP. Conversely, higher awareness and lower willingness to use PrEP in HIC demonstrates more realistic expectations for use versus hypothetical willingness for use. The focus on willingness and awareness of PrEP in LMIC demonstrates the infancy of PrEP implementation in LMIC, whereas the focus on effectiveness, adherence and cost-effectiveness in HIC shows PrEP to be further along the implementation continuum. Motivating governments to provide PrEP proves to be a barrier for its implementation due to the high and additional costs of PrEP, despite its cost-effective and even cost-saving abilities.

Contribution statement The author made substantial contributions to the work, drafted the work and gave final approval of the version to be included in Inspire.

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Review

The impact of diabetic ketoacidosis on cognitive function and its importance in forming prevention strategies

Ishani Rakshit
Year 3, Medicine, University of Exeter
Email: ir264@exeter.ac.uk

Abstract

Diabetic ketoacidosis (DKA) is a potentially serious complication of diabetes that emerges following an absence of insulin, and prevalence is rising. As such, clinicians have a responsibility to recognise patients that might be at higher risk of DKA and implement preventative strategies wherever possible. Given that diabetes has a heavy self-care burden, having adequate cognitive functioning (CF) is essential to preserve good health and minimise DKA episodes. DKA has been associated with acute cognitive impairments within specific domains and recurrent episodes may even successively further reduce CF. Changes in CF should be considered in the long-term management of diabetes, especially for older patients who are at greater risk of DKA recurrence. Diabetes-management education programmes might benefit from implementing different modes of delivery for individuals with reduced CF or considering DKA-specific programmes for these patients. Suitable support plans can potentially reduce the incidence of DKA, thus, benefitting public health.

Abbreviations

CF - Cognitive function
DKA - Diabetic ketoacidosis
EF - Executive function
NAA - N-acetylaspartate
PSE - Psychomotor efficiency
T1D - Type 1 diabetes

Introduction

Since 1996, the prevalence of diabetes in the UK increased from 1.4 million to 3.5 million patients.[1] Diabetic ketoacidosis (DKA) is a serious complication of diabetes following an absolute absence of insulin, predominantly affecting type 1 diabetes (T1D) patients.

> *In recent years, the incidence of DKA in T1D patients at initial diagnosis has increased from 35% in 2007 to 58% in 2018.[2]*

Therefore, there is a responsibility imposed upon clinicians to recognise patients who might be at a higher risk of DKA and implement preventative strategies wherever possible. Given that diabetes has a heavy self-care burden, having adequate cognitive functioning (CF) is essential to preserve good health and minimise DKA episodes. There is some evidence to suggest that DKA is linked to reductions in CF. Poor CF may impact a patient's ability to self-care and increase risk of DKA episodes.

What is DKA?

> *Characteristic presentations of DKA are hyperglycaemia, ketonaemia and metabolic acidosis.*

DKA is most commonly caused by poor concordance with insulin therapy often after initial T1D diagnosis or following infections of the chest/urinary tract.[3] Insulin deficiency prevents the uptake of glucose into metabolic tissues, which results in hyperglycaemia.[3] This forces tissues to rely on other sources of energy such as triglycerides and

amino acids, which form ketones as a by-product of metabolism.[3] Prolonged insulin absence causes a build-up of ketones in the blood, which results in metabolic acidosis. DKA may induce symptoms of polyuria, vomiting and abdominal pain. Additionally, it has been shown that patients of all ages demonstrate changes in their CF.[2,4] DKA can be accompanied by confusion, loss of consciousness and cerebral oedema,[3] further reinforcing that DKA may influence neurological functioning within the brain.

Why is it important to understand the link between DKA and CF?

CF can be greater conceptualised by differentiation into functional domains - some key areas being attention, executive function and memory.[5] Impairment within any domain may impact an individual's ability to lead an independent life. Diabetic patients have an arduous self-care obligation, of which responsibilities include daily monitoring of blood glucose and taking insulin at the correct dose and time.[6] Poor CF has the potential to decrease adherence to insulin therapy. Hence, a vicious cycle can emerge of DKA reducing CF, a resultant worsening of diabetes self-management and thus increased likelihood of DKA incidence.

Previous DKA is a known risk factor for recurrence - approximately 20% of people who experience DKA at the time of initial T1D diagnosis might experience sequential episodes.[2] In older adults, the risk of experiencing another DKA episode is even greater at 34%.[2] As the life expectancy of T1D patients increases, there is an increasing population of older adults living with the disease, which may help to explain why a higher number of older adults are experiencing successive DKA events.[2] The normal ageing process has shown links with declining CF.[7] When combined with the greater risk of mortality that older DKA patients face following an event,[8] diabetics within this age group appear to be particularly vulnerable to poor health outcomes.

> *Gaining a better understanding of the cognitive impact following DKA might lead to more effective management plans, especially for the most high-risk patients.*

This review will consider which areas of CF are most impacted following DKA, and how DKA recurrence and age might affect prognosis. Some ideas to help reduce the onset of DKA will also be explored. Gaining a better understanding of how cognitive states may be impacted by DKA could aid clinicians in creating an effective management plan to reduce recurrence and severity of episodes in diabetic patients.

Which specific areas of cognition are affected in DKA?

Executive function (EF) is an important measure of CF. It refers to a group of skills, such as attentional control and task-planning, that are needed to coordinate cognitive processes to achieve a common goal.[9] Impairments in EF can affect an individual's ability to complete daily routines. This might lead to difficulty for patients in keeping to a schedule of diabetes management. Children with a history of DKA have shown lower EF than their age-matched counterparts, with higher glycated haemoglobin correlating with lower CF.[4] This suggests that poor glycaemic control directly affects CF. These results have been replicated in older adults (mean age = 67), who showed significantly reduced CF, especially within EF and psychomotor efficiency (PSE).[2] PSE describes the overall speed and coordination of the cognitive system. It is an important factor to consider since changes to information processing abilities may create feelings of being overwhelmed, which can be expressed as distress or anxiety. These emotional consequences are likely to have an impact on the extent to which an individual is able to carry out self-care.

It is imperative to note that the previously mentioned studies on older adults and children[2,4] did not have long-term follow-up aspects, so it is unclear as to how long the reduced cognitive states presenting at the time of the study would persist. A study performed on T1D adults showed that higher glycated haemoglobin was linked to acutely reduced PSE, however, there were no long-term declines in CF.[11] These patients also experienced successive severe hypoglycaemic episodes, which further emphasises the idea that poor glycaemic control is associated with cognitive difficulties, but the direct effect of hyperglycaemia on the participants is not clear. Moreover, this study considered DKA in the context of T1D, which although common to most DKA patients, is not an exclusive feature and so long-term studies specific to broader DKA patients is required.

Does frequency of DKA affect CF?

There is evidence to suggest that repeated DKA may lead to progressively greater neurological injury, which may in turn affect CF.[12] A case study following an adolescent T1D patient found that recurring DKA was linked to reduced N-acetylaspartate (NAA).[12] NAA is a neurological marker which is affected by decreased neuronal function or neuronal loss.[12] This indicates that DKA directly impacts the structural integrity of neurons. Although NAA levels did not return to prior baseline levels, there was some recovery shown in readings taken 3 days after the episode, which suggests that the time period acutely following DKA is crucial to ensure maximum neuronal recovery. Total recovery was greater following the first episode, indicating that with successive DKA episodes the extent of recovery diminishes. Neurocognitive testing was not performed in this study, so it is not possible to delineate how DKA may have affected CF.

A study following an older cohort, found that those with recurrent episodes were 3.3 times more likely to have lower CF than those who had never experienced DKA.[2] This study only considered DKA which resulted in hospitalisation; DKA that is less serious in nature might not have as great an effect on CF. Moreover, recurrent DKA in older patients, especially of the nature that requires hospitalisation, might have more extreme consequences than in younger patients. Further research will be necessary to gain a better understanding of the effect of repeated DKA episodes on CF in a wider demographic.

The impact of age on DKA incidence

Normal ageing is associated with lower CF in healthy patients,[13] so in older DKA patients the rate of decline may be further exacerbated. Moreover, older populations have a higher risk of experiencing repeated episodes.[2] Successive insult to CF following recurrent DKA might further impose difficulties in effectively self-managing their diabetes and preventing future DKA. Patients within this age group are more likely to experience DKA-related hospitalisations, which could be due to health fragilities that can accompany old age. With older age comes greater likelihood of experiencing multiple comorbidities,[8] which is likely to increase risk of complications. Moreover, patients managing multiple comorbidities are often burdened with polypharmacy. Managing multiple medications alongside insulin could be challenging to individuals, especially if cognitively impaired. These factors may all contribute to the greater risk of DKA-related mortality within older populations.[8] Comorbidities, ability to self-care and CF all need to be considered by clinicians when implementing DKA prevention methods for this age group.

Whilst older populations are at greater risk of recurring and more serious DKA, young adults have been observed to experience more singular DKA episodes.[4] Young adults are more likely to experience mental health challenges, to use tobacco and less likely to see a primary care provider than older adults – these are all contributing factors for poor glycaemic control.[14] These are largely modifiable risk

factors, so perhaps greater knowledge of how lifestyle factors impact diabetes could help to reduce DKA incidences in this age cohort. Eating disorders are a lesser known risk of DKA. Diabulimia is the colloquial term for a specific eating disorder affecting T1D patients, especially young females.[15] These patients might knowingly omit insulin with the goal of weight loss, and as a result may experience DKA. Encouraging clinicians to include psychological evaluations alongside routine physical examinations of diabetic patients may improve diabulimia recognition. Appropriate psychological interventions may help to prevent avoidable DKA episodes in these patients.

Preventing DKA

Ensuring that patients receive appropriate care could reduce the risk of DKA events. Personal modifications to patient care, such as home visits for those experiencing difficulty in attending GP appointments, could improve wider access to healthcare. This may be especially relevant as fragmentation of healthcare is associated with greater risk of recurrent DKA.[8] A report evaluating DKA management from patient perspectives found that "prevention of recurrent episodes" was important for patients. Additionally, "providing information for what to expect over the course of treatment for diabetic ketoacidosis" was considered a good step for reducing their anxieties and fears.[16] As such, patients might also benefit from a clear breakdown of what to expect at their initial diagnosis of diabetes in order to reduce anxieties - this might be helpful in individuals prone to feeling overwhelmed. Given that elevated glycated haemoglobin is linked to reduced PSE,[10] which itself is associated with feeling overwhelmed, this might be especially relevant for diabetic patients that struggle with glycaemic control.

> *Diabetes self-management education can give patients relevant knowledge to prevent recurrent DKA.*

Emphasis should be placed on tackling unexplained hyperglycaemia and ketosis at home, which can emerge when patients get unwell with other illnesses - this is known as sick day management.[16] Many patients perceive this as an important category to help them feel better about managing their condition.[16] Improved knowledge on how to manage their condition has been associated with reduced hyperglycaemia, enhanced treatment adherence and improved abilities in using technological devices such as insulin pumps.[17] Indeed, structured education programmes have been shown to reduce DKA hospitalisations.[6]

Various diabetes education courses currently exist within the UK,[18] but access may be gated behind clinical referral or socioeconomic factors. Furthermore, DKA patients might have already participated in a programme at the time of their T1D diagnosis and feel they no longer need to be educated on how to manage their condition. There do not appear to be specific programmes for those who have previously experienced DKA, so perhaps arranging such schemes could be valuable. Moreover, DKA patients with reduced CF may benefit from different forms of educational delivery to make the information more accessible - this is something clinicians should consider when forming management plans. When CF is impaired so significantly that educational programmes are ineffective, further support might need to be explored, such as district nurses who can provide in-home care and administer insulin themselves.[19]

Conclusion

At present, the literature regarding DKA and CF remains relatively sparse. Whilst DKA has been associated with acute cognitive impairments, most notably in EF and PSE, the long-term effects remain unclear. DKA episodes might be more common in younger patients but older cohorts have a greater risk of mortality - these age cohorts might require additional care in managing their diabetes to prevent episodes.

There is some evidence that recurrent episodes can successively further reduce CF. This needs to be considered by clinicians, especially for older patients who are at greater risk of recurrence. Structured diabetes-management education programmes have been shown to reduce DKA episodes and improve patient satisfaction. Different modes of delivery might be appropriate for those that are unable to engage with these programmes due to, for example, low CF. Moreover, the introduction of DKA-specific programmes may prove more efficacious within DKA patients. Suitable support plans can potentially reduce the incidence of DKA, thus, benefitting public health.

Acknowledgements I would like to thank the University of Exeter for supporting me in writing this article, especially my supervisor Dr Alice McLoughlin for helping me better understand the disease profile of diabetes.

Contribution statement The author made substantial contributions to the article and was responsible for drafting the work. The author gave approval for the article to be included in Inspire.

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Review

Reversible cerebral vasoconstriction syndrome: an underestimated cause for thunderclap headache in emergency settings

Hateem Rafeeque
Year 3, Medicine, University of Exeter
Email: har205@exeter.ac.uk

Abstract

Thunderclap headache (TCH) is severe and occurs rapidly. It can have many underlying causes with similar presentations causing confusion among clinicians. The most serious underlying condition is a subarachnoid haemorrhage (SAH), which takes priority. Another increasingly recognised cause of a TCH is reversible cerebral vasoconstriction syndrome (RCVS). RCVS can be diagnosed with angiography after an SAH is excluded. RCVS and its differential diagnoses have very similar presentations, thereby making the diagnosis of RCVS difficult; however, there are specific differences that can be observed to correctly identify the condition. RCVS has classical presentations and triggers that should be examined in a comprehensive history to avoid misdiagnosis and unnecessary treatment. Clear guidance on diagnosing RCVS is required, especially in emergency settings. RCVS is generally assumed to have a positive outcome, however, some patients experience further complications such as strokes, seizures, SAHs and, even, death. Because of this, patients with RCVS should be monitored regularly. RCVS can also have self-resolving temporary worsening, which clinicians should bear in mind. Treatment for RCVS aims to manage symptoms and remove any potential triggers. However, there is very limited pharmacological-based evidence for therapy for RCVS and further research is required to determine the best treatment for this condition.

Abbreviations

CAD - Cervical artery dissection
CSF - Cerebrospinal fluid
CT - Computed tomography
CTA - Computed tomography angiography
DSA - Digital subtraction angiography
MRA - Magnetic resonance angiography
PACNS - Primary angiitis of the central nervous system
RCVS - Reversible cerebral vasoconstriction syndrome
SAH - Subarachnoid haemorrhage
TCH - Thunderclap headache

Introduction

Headaches are the most common A&E presentation in the UK.[1] Headaches that are severe and sudden headaches can indicate a serious underlying pathology.[2,3] A potentially life-threatening headache that often presents in A&E patients is a thunderclap headache (TCH): a throbbing, debilitating headache that occurs spontaneously, peaking within one minute, and which can last for weeks later.[4] Primary TCH is diagnosed when all other aetiologies are excluded.[5] TCH has many secondary causes, the most prominent being a subarachnoid haemorrhage (SAH). Another important,

but less-well identified cause for TCH is reversible cerebral vasoconstriction syndrome (RCVS), which occurs when cerebral arteries constrict and dilate abruptly.[6] Symptoms associated with TCH in RCVS can include nausea/vomiting, photosensitivity and phonophobia.[5,6] The incidence of RCVS is unknown, however, it may be more prevalent than realised, possibly due to errors in the diagnosis of RCVS, particularly in emergency settings.[5,7-9] There is no single definitive cause for RCVS, although pregnancy and vasoactive drugs have been linked its development.[7,10] RCVS is primarily diagnosed with radiological findings of segmental cerebral vasoconstriction within 12 weeks of the onset of a TCH. This can be done by digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA).[6,11]

In RCVS, the TCH typically reoccurs an average of four times over four weeks and may be accompanied by neurological deficits.[14] Though most clinical outcomes of RCVS appear to be benign, there are potential future complications, such as strokes, seizures and SAH.[5] A diagnosis of RCVS may help individuals to prepare for potential associated future difficulties. An inaccuracy in the diagnosis of RCVS may have serious complications for the patient later in life.

This review will discuss RVCS as a cause for TCH and how it is managed in emergency settings. This review will be constructed in 4 parts: (1) characteristics and investigations for RCVS; (2) RCVS compared with differential diagnoses of TCH; (3) management and consequences of untreated RCVS; and (4) diagnosis in emergency settings and potential reasons for errors in diagnosis.

Literature search

Articles utilised in this review were predominantly collected from the online database PubMed. Additional online sources used were The Lancet and Google Scholar. Key terms searched for were "reversible cerebral vasoconstriction syndrome" and "thunderclap headache". These terms were used in conjunction with "emergency setting", "diagnosis", "differential diagnosis", "management" and "prognosis". Boolean factors (i.e. "NOT", "AND" and "OR") were used to create an algorithm with the keywords to filter out appropriate papers on PubMed. Articles were excluded if the full text was not freely available and if the publication was not in English. Some papers were also found through searching references of systematic reviews and meta-analyses. Based on relevance, and the inclusion and exclusion criteria, a total of 25 studies were included.

General information and statistical data on RCVS were retrieved from The National Institute for Health and Care Excellence and the National Health Service websites.

Characteristics and investigations for RCVS

The main presentation of RCVS is a TCH, which often occurs with several conditions, including SAH, primary angiitis of the central nervous system (PACNS), cervical artery dissection (CAD) and central venous thrombosis (see **Table 1**). In RCVS, the TCH usually occurs without any additional symptoms, is bilateral and short-lived.[5,14] Common triggers for RCVS have been identified, including the use of vasoactive drugs and antimigraine medication, sexual activity, postpartum state, and selective serotonin reuptake inhibitors.[7,10] Identifying these triggers using a detailed history could be used to suggest RCVS. Moreover, a correct diagnosis of RCVS could prompt patients to steer clear of these triggers to reduce the chances of a TCH. Angiography can be used to diagnose RCVS; however, studies have shown that angiography is not routinely performed in patients with an undetermined TCH.[2] Ducros *et al*. recommends performing a second angiogram if RCVS is suspected and the first angiogram is normal.[14] This is due to the first angiogram usually being performed within 1 week of the onset of symptoms whilst the maximum vasoconstriction of the middle cerebral arteries occurs at around 16 days after onset of symptoms.[14]

Table 1. Differential diagnosis of a TCH.[6,15]

	Presentation	Diagnosis
SAH	• Sudden onset of headache • Neck pain and neck stiffness are common • Transient loss of consciousness	• CT scan within 6 hours • Lumbar puncture after 6 hours
PACNS	• Usually subacute/chronic onset of headache	• Angiography • Abnormal CSF
CAD	• Neck pain and headache • Risk factors: recent trauma, connective tissue disease, hypertension, migraines and large vessel arteriopathies	• Head and neck CTA
Cerebral venous thrombosis	• Associated symptoms include papilledema, seizures, neurological deficit, distorted mental state • Usually aged <50 years • Hypercoagulopathy following events (e.g. surgery, postpartum) increases risk	• CT or MR venogram

CT, computed tomography; CTA, computed tomography angiography; CSF, cerebrospinal fluid; MR, magnetic resonance.

RCVS compared with differential diagnoses of TCH

Symptoms associated with a TCH are similar in many of the differential diagnoses of this condition, and to RCVS, which makes it difficult to distinguish between the conditions without additional imaging. Several differences between the clinical manifestations of RCVS and its differential diagnoses have been observed[15] and are discussed below.

SAH SAH is the most prevalent underlying cause for TCH.[16] It has been found that 50% of patients with SAH experience TCH.[17] SAH and RCVS present very similarly, although some differences in their clinical manifestations have been reported. TCHs in SAHs are usually unilateral on the side of the haemorrhage, whereas TCHs in RCVS is typically generalised or occipital. Additionally, TCH in RCVS tends to be shorter-lived than in SAHs.[4, 6, 15]

Without appropriate treatment, an SAH has a substantial mortality and morbidity rate; therefore, initial assessment of TCH must focus on SAH.[17] Computed tomography (CT) and lumbar puncture are highly sensitive preliminary assessments to detect SAH in patients with TCH. However, many differential conditions, including RCVS, cannot be identified by these assessments alone. If the CT and lumbar puncture are negative and SAH is ruled out, it is advised to perform an angiogram.[15]

PACNS PACNS is a rare inflammatory disease of the brain and spinal cord.[6] Distinguishing between PACNS and RCVS can be extremely difficult as PACNS patients present with a TCH and have similar angiograms.[10] Additional testing, such as a lumbar puncture, may be useful as abnormalities in cerebrospinal fluid (CSF) can be observed in ~90% of patients with PACNS, whereas CSF is usually normal in RCVS patients.[11] Analysis of symptoms may also aid in distinguishing between the two. For example, multiple TCH has never been reported in PACNS but is a classic feature of RCVS.[10] Additionally, symptoms gradually develop in PACNS, while symptoms in RCVS occur rapidly.[7] Furthermore, vasoconstriction is typically reversed within days after onset in RCVS but this is not the case for PACNS.[9,11]

CAD The typical presentation of CAD differs from RCVS in several ways. Headache in CAD is usually accompanied by neck, ear and face pain, which are not identifying features of RCVS.[14] Patients with CAD can also present with Horner's syndrome, comprised of miosis, ptosis and anhidrosis.[7] Testing for suspected CAD should include

ultrasound and angiography.[18] Also, it is important to note that CAD has been shown to be comorbid with RCVS;[5,18] although, it is unknown whether RCVS causes CAD or vice versa.

Management and consequences of untreated RCVS

RCVS should be managed by temporarily avoiding potential triggers, such as sexual intercourse, vasoactive drugs, and exercise.[7,10] Symptomatic treatment, such as analgesia and rest, are recommended. Blood pressure monitoring is also suggested.[14] Furthermore, it is fundamental to support patients' emotional and mental wellbeing. Suggested pharmacological treatment is comprised of various combinations of calcium channel blockers, corticosteroids, and intravenous magnesium.[19] Nimodipine, a calcium channel blocker, has been found to decrease the intensity and frequency of headaches in selected patients.[20] However, there is no data on the effectiveness of nimodipine in the treatment of RCVS from randomised control trials.[21] Glucocorticoids are sometimes used to treat RCVS, but some studies show no benefit or, even, potential worsening of the condition.[9] This is complicated by glucocorticoids being beneficial in the treatment of PACNS, which presents very similarly to RCVS.[22] Delaying treatment of PACNS for a few days with glucocorticoid steroids has not been found to increase adverse effects; thus, glucocorticoids may be held off until a more definitive diagnosis is achieved. Subsequently, if RCVS is diagnosed, glucocorticoids should be avoided. Intravenous magnesium has been shown to suddenly relieve symptoms of RCVS in 2 patients in whom treatment with calcium channel blockers and corticosteroids had not been successful.[23] This indicates a potential area of research for the treatment of RCVS.

The prognosis of RCVS is generally thought to be good as most patients' headaches resolved within days or weeks without any lasting symptoms.[13] However, studies have shown that some patients experience further complications post-diagnosis.[9,14] Patients have been reported to develop long term vasoconstriction, which led to ischaemic stroke and, in some cases, death.[13,19] Haemorrhagic strokes have also been reported after RCVS, with the underlying mechanism being uncertain.[19] Other possible subsequent conditions include seizures and SAH.[5] To prevent these outcomes, clear guidance on monitoring patients diagnosed with RCVS should be created. Furthermore, additional research is required to elucidate the mechanisms behind RCVS-associated strokes, seizures, SAHs and mortality. This may aid in the development of prophylactic measures for patients diagnosed with RCVS.

Some patients have temporary worsening that self-resolves.[19] Katz *et al*. reported that most participants with clinical worsening recovered shortly after the time of worsening.[19] With accurate diagnosis, clinicians can anticipate reversible worsening and prevent unnecessary testing and treatment.

Diagnosis in emergency settings and potential reasons for errors in diagnosis

Studies have demonstrated the inadequacy of the diagnosis of RCVS, particularly in emergency settings.[2] Kim *et al*. found that patients with RCVS needed to be seen by emergency physicians 4.7 times, with symptoms persisting for 9.3 days on average before receiving a precise diagnosis.[2] It was suggested that this may have been due to similar presentations to those of ruptured aneurysms.[2] These findings are not truly representative of the population as the data are derived from a small cohort of just 18 participants. Despite this, the study presents confusion among clinicians in the diagnosis of RCVS. Miller *et al*. show how appropriate imaging can be used to distinguish differential diagnoses from RCVS.[10] If RCVS is suspected after ruling out SAH, Tan and Flower recommend first performing an MRA or CTA based on availability, following this with a DSA if the MRA/CTA is negative and RCVS is still suspected.[24]

Furthermore, Ducros *et al*. highlighted a key issue in the diagnosis of RCVS, with some patients having normal MRAs upon initial testing.[5] There was a variation of between 1 and 2 weeks from the onset of headache and visible vasoconstriction on MRA.[5] This shows that an initial normal MRA cannot rule out RCVS. Moreover, physicians may struggle to make an accurate diagnosis due to the intensity in an emergency setting. To help with this, an awareness of the possible causes of TCH may be helpful if SAH is ruled out. A summary sheet with the various conditions and their presentations could be compiled for reference in emergency departments.

Conclusion

RCVS is becoming more recognised. Currently, there are still no clear guidelines for the diagnosis and management of RCVS. It is recommended to perform an angiogram after an SAH has been ruled out, with peak vasoconstriction being visible at 16 days after onset of symptoms. There are several triggers for RCVS that should be avoided in individuals with suspected or diagnosed RCVS. In most instances, RCVS self resolves without further complications; however, RCVS can increase the risk of stroke, SAH and death, which should be monitored. Furthermore, RCVS has similar presentations to other conditions that present with a TCH, although there are certain differences that can be observed. There is no evidence-based pharmacological treatment for RCVS; hence, more research is required to identify appropriate treatment. A potential area of future research is magnesium infusion in the treatment of a TCH in RCVS. Management should include supportive measures, such as analgesia, avoidance of triggers and support for each patient's mental well-being.

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Review

COVID-19 and cardiac surgery: investigating the effect of short-term delay of elective cardiac surgery on mortality rate and hospital capacity

Mohamad Aljarad
Year 2, Medicine, Plymouth University
Email: mohamad.aljarad@students.plymouth.ac.uk

Abstract

The Royal College of Surgeons recently published new guidelines and protocols attempting to reduce the risk of COVID-19 for patients and staff without compromising the quality of care and treatment for patients who require cardiac surgery. The guidelines introduced a new classification system to categorise patients based on their need of surgery, which led to the postponement of all elective cardiac surgery. This article investigates the effect of this categorisation system on cardiac surgery, focusing firstly on the effect of short-term delay of elective cardiac surgery on mortality rate and secondly how postponement may have helped establish a COVID-19-free environment and increased hospital capacity. A search was conducted using the PubMed database and five articles were selected. It has been found that the new guidelines helped to increase hospital capacity and establishing a COVID-19-free environment. Due to the lack of evidence, it is still unknown whether the new guidelines may have led to higher mortality rates. It is concluded that further research is needed to investigate the effect of short-term delay of elective cardiac surgery on mortality rate.

Abbreviations

ACE2 - Angiotensin-converting enzyme 2 receptors
CABAG - Coronary artery bypass graft
CVD - Cardiovascular diseases
ICU - Intensive Care Unit
PCI - Percutaneous coronary intervention

Introduction and background information

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a significant effect on global healthcare services, requiring the need for unparalleled healthcare system adaptations.[1] With the rapid increase in COVID-19 cases, and the drastic strain on healthcare systems, it was important to reallocate intensive care services to cope with the accelerating burden raised by COVID-19. As of March, 2020, in the UK, 97 patients needed hospital admission every day and, of those, 76 patients needed ventilation.[2] As a result, the pandemic has led to a lack of ventilators, intensive care units, personal protective equipment, and health care staff.[2] These limitations have potentiated the need to introduce drastic new measures to the medical care of surgical patients, especially in cardiac surgery, which is largely dependent on intensive care resources.[2]

A meta-analysis of observational studies evaluating cardiovascular complications in hospitalised COVID-19 patients found that those with pre-existing cardiovascular disorders were at higher risk of mortality.[3] In addition, an exacerbated course of pneumonia was observed in patients with underlying cardiovascular diseases (CVD), which required admission to the intensive care unit (ICU) and prolonged hospital stay. SARS-CoV-2 uses angiotensin-converting enzyme 2 receptors (ACE2) to enter the host cell. The exacerbated course of pneumonia in those with CVD has been attributed to the increased expression of ACE2 receptors as a consequence of renin-angiotensin-aldosterone inhibitors widely used in the treatment of cardiovascular conditions. Higher expression of ACE2 receptors might

lead to more severe SARS-CoV-2 infection and explain why patients with pre-existing CVD have a higher mortality rate.[4] Establishing a COVID-19-free environment was, therefore, deemed key to reducing the risk of complications and rate of mortality in those with CVD.

The new guidelines released by the Royal College of Surgeons in the UK

In order to establish a safe environment and increase hospital capacity, a nationwide assessment was carried out in the UK. The resulting plan involved converting surgical intensive care units into overflow intensive care units to increase capacity for patients with COVID-19. In addition, building centralised units for subspecialties, such as cardiac surgery, aimed to provide a safe but limited environment for patients who needed to undergo cardiac surgery. This reconfiguration resulted in a significant reduction in the number of operations that could be carried out per day. The reduction was up to 80% in some centres meaning that many elective surgeries had to be cancelled to focus on life-saving procedures.[5] Therefore, a new categorisation system was developed to redefine the urgency of elective cardiac surgeries; this classified patients into four levels (**Table 1**).[6,7]

Table 1. The four urgency levels of elective cardiac surgeries.[6]

Level of urgency	Required time for surgery
Level 1	Surgeries needed within 72 hours
Level 2	Surgeries that can be postponed up to 4 weeks
Level 3	Surgeries that can be delayed up to 3 months
Level 4	Surgeries that can be deferred for more than 3 months

It is important to mention that postponement of elective cardiac surgery was not applied in the UK alone but mirrored an international call to postpone elective cardiac surgery.[5] While these new guidelines may help to provide a COVID-19-free environment and prevent hospitals from being overwhelmed, postponing elective surgery may increase the risk of cardiovascular deterioration and, also, mortality rate. This article examines whether postponing elective cardiac surgery helped in establishing a COVID-19-free environment and investigates the effect of short-term postponement (less than 52 weeks) of elective cardiac surgery on mortality rate.

Literature search

A search of the peer-reviewed database PubMed was conducted using a combination of the terms "COVID-19", "elective cardiac surgery", "postponing", "short waiting times", "COVID-19 free environment" and "hospital capacity". Only articles in the English language were included. No exclusions were made based on publication date. The literature search results were screened in two stages; the first stage involved initial inspection of the study titles and abstracts to identify relevant articles and, as a result, 132 articles were excluded. The second stage involved in-depth reading of the full-text articles, which led to the exclusion of 12 articles (**Figure 1**). In total, 5 studies were found that fit the search criteria (see **Table 2**).

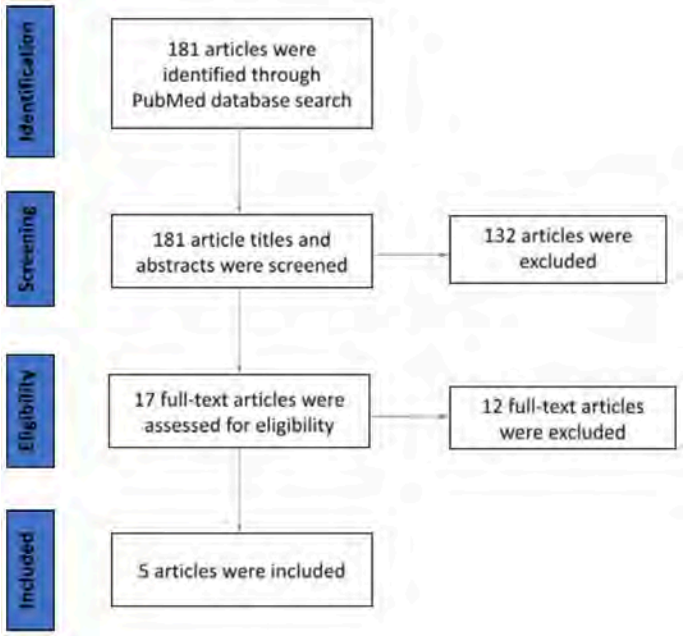

Figure 1. Flow chart of search strategy. A flow chart illustrating the search strategy used to identify articles relevant to the effect of postponing elective cardiac surgery on mortality rate and hospital capacity.

Table 2. A summary of the studies found by the literature review.

Selected studies	Research method(s)	Sample size (n)	Content/ theme
Harky *et al*, 2020[8]	A survey of patients who underwent aortovascular intervention during the COVID-19 pandemic	59 patients	Investigating the outcomes and characteristics of patients who underwent elective cardiac surgery
Head *et al*, 2017[9]	A systemic review and meta-analysis of 22 articles	66410 patients	Exploring the effect of different waiting times and adverse event rates
Metelmann *et al*, 2020[10]	A two-centre analysis of postponed cardiac operations	109 patients	Investigating postponed elective cardiac surgery
Peters *et al*, 2020[11]	A descriptive study		How postponing elective cardiac surgery helped in increasing hospital capacity
Sobolev *et al*, 2006[12]	A population-based prospective study	8325 patients	The effect of delaying cardiac surgery

Establishing a safer environment and increasing hospital capacity

In a cohort study, the outcomes of 29 elective cardiac surgery cases were examined at Liverpool Heart and Chest Hospital in the UK, analysing patient outcomes after applying the new guidelines. Post-operatively, none of the patients experienced COVID-19-related pneumonia nor were any deaths attributed to COVID-19 infection. The results were seen as a validation of the new categorisation system, which helped to prioritise patients with life-threatening conditions and provide a safer environment.[8]

During the COVID-19 pandemic in March 2020, at New York–Presbyterian Weill Cornell Medical Center, the demand for beds in ICUs and for mechanical ventilation devices exceeded baseline capacity. Postponement of elective surgeries allowed conversion of operating rooms not in use into ICUs. This involved repurposing ventilation and anaesthesia machines for patients critically ill with COVID-19. In addition, it yielded 60 extra beds, increasing hospital capacity by 52% percent. This study provides further evidence in support of the new categorisation system and suggests that without the cancellation of elective surgeries, increased ICU capacity would not have been possible.[9]

The new guidelines may have increased the mortality rate

After the publication of the new categorisation system, surgeons were confronted with the difficult decision of cancelling or postponing elective surgeries. It is clear that 'elective' does not mean a non-essential procedure; therefore, delaying elective surgeries might have increased the rate of mortality and morbidity. This argument emerges from previous studies, including randomised trials and observational studies estimating the conditional probability of death in relation to delay times for patients who required cardiac revascularisation surgery. One prospective study included 3825 patients registered to undergo cardiovascular pulmonary bypass graft (CABAG). The study looked at the number of patients who died when CABAG was not done at specific times over 52 weeks of taking the decision to postpone treatment. The study concluded that as the waiting time increased, probability of death increased.[10] However, the waiting time in this study was up to 52 weeks, which is much longer than the waiting time during the COVID-19 pandemic. An alternative comparison is a study that assessed the effect of short-term postponement of elective surgeries on mortality rate.[11] In this study, data was analysed from two centres in Germany (the University Hospitals of Leipzig and Greifswald). In Leipzig University Hospital, 89 elective operations were postponed, while in Greifswald, 92 elective procedures were postponed from March 16th to April 20th 2020. The postponement decision was made following the new guidelines released by the German Society of Surgery.[11] The research revealed that one patient with severe obesity died during the postponement period due to cardiovascular complications but that, overall, short-term delay did not lead to higher rates of morbidity and mortality. It is important to note some limitations of this study, particularly that both hospitals had very low COVID-19 infection rates, which ensured a high capacity of ICUs and ventilation units for performing surgery, even at short notice. In addition, data from out-patients who had their surgeries postponed were not included. Therefore, based on these data, a link between the delay of elective surgery and mortality rate is inconclusive.

A meta-analysis of 22 studies investigated the rate of adverse events while awaiting percutaneous coronary intervention (PCI) and CABAG.[12] The study found that mortality in patients awaiting revascularisation surgery was infrequent but that mortality rates were higher in a specific group of patients. The key findings of the study were that the most significant predictors of death were the patient's status, namely the severity of angina and left ventricular dysfunction. The study results highlight the significance of recommending a maximum waiting time for CABAG and PCI surgeries. One of the limitations in trying to establish the effect of waiting time on mortality rate is the variability in waiting times between studies, coupled with different inclusion criteria and study designs. Therefore, further investigations and studies are required to establish the effect of short-term delay of elective surgeries on mortality rates.

Evaluation

Undoubtedly, the pandemic has transformed the practice of cardiac surgery around the world. Shortage and limitations of health-care facilities led to the introduction of new guidelines aimed to utilise resources, prioritise patients and provide safer environments. Preliminary evidence suggests that the new guidelines released by the Royal College of Surgeons led to a reduction in the volume of operations, which helped to increase hospital capacity to treat patients critically ill with COVID-19.[8] This also helped minimise the spread of COVID-19 in hospitals, providing a safer environment with reduced risk of COVID-19 infection.[9]

With regard to the link between waiting times and mortality, evidence supports prolonged waiting times being linked to higher rates of mortality. However, it is important to focus on the impact of short waiting time (less than 52 weeks) because, during the pandemic, waiting times were not very long. Due to the lack of evidence, it was not possible to reach to a definitive conclusion regarding the impact of a short delay of elective cardiac surgery on mortality rate.

Since the continuity of surgical excellence is needed in any circumstances, more plans should be developed for any potential crisis in the future. The first step to achieve this is by exploring the impact of COVID-19 on the surgical field, which will allow us to fill major knowledge gaps that currently exist. For instance, more research is needed to examine the impact of short-term delay of elective surgeries on mortality rate; this would enable us to determine the optimal time to perform elective surgical interventions. As a result, the Royal College of Surgeons might then be able to include maximum waiting times in their guidelines.

Conclusion

During the pandemic, the Royal College of Surgeons reacted quickly and effectively despite the shortage of equipment and amid the uncertainty of the situation. The new guidelines they released were beneficial as they led to a reduction in the volume of operations and, consequently, the repurposing of operating rooms into ICUs, increasing hospital capacity and reducing risk of COVID-19 infection. The effect of short-term delay of elective surgery on mortality rate is still unknown. More research is needed in order to fill this knowledge gap and develop new strategies and guidelines for any similar crisis in the future.

Acknowledgements I would like to thank Dr John Chilton (Peninsula Medical School, University of Plymouth, UK) for his supervision and guidance. I am also very thankful to the editors of the INSPIRE Student Health Sciences Research Journal for providing constructive feedback.

Contribution statement The author of this article has contributed substantially to the conception, design, drafting and editing of this work. Final approval of the version for inclusion in Inspire has been provided by the author.

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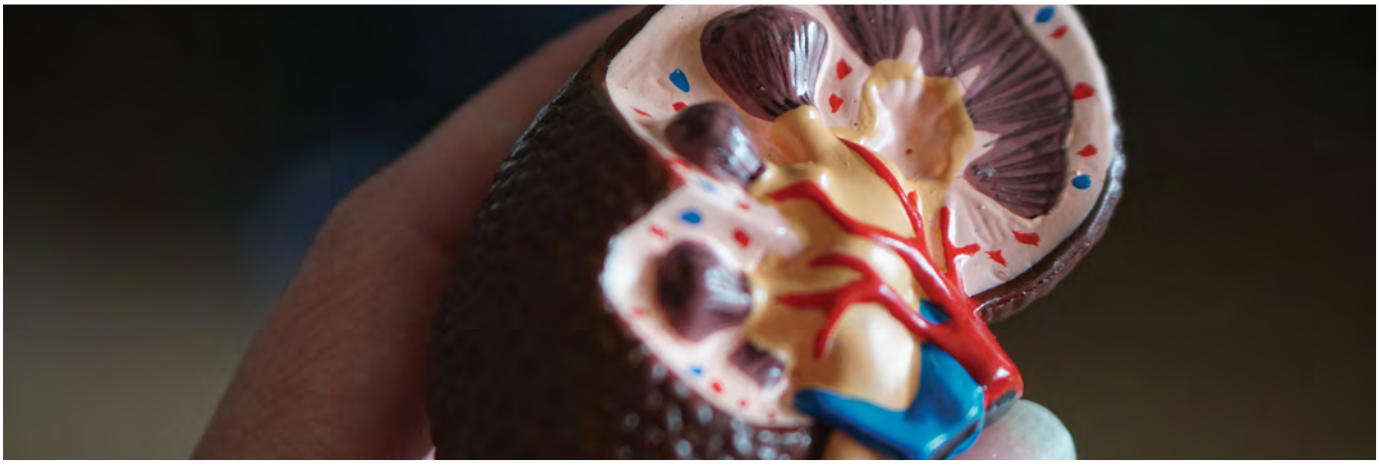
Review

Does the Notch signalling pathway play a role in hypoxia-induced renal fib osis?

Kesri Gajadhar
Year 3, Medicine, University of Exeter
Email: kag223@exeter.ac.uk



Abstract

Chronic kidney disease (CKD) has been estimated to affect millions of people in the United Kingdom. As such, much research has been conducted and the Notch signalling pathway (NSP) has been identified as a probable factor involved in triggering fibrogenesis in the kidneys, as a result of hypoxia. This review primarily aims to explore whether or not the NSP plays a role in hypoxia-induced renal fibrosis. Experiments have found that hypoxia triggers the NSP by up-regulating levels of the intracellular domain of the Notch receptor and expression of its ligand. In succession, in vitro experiments, which involve using components of an organism that have been removed from the usual biological surroundings, have concluded that the NSP produces changes typical of epithelial-to-mesenchymal transition (EMT). Conversely, in vivo experiments conducted on mice have noted that Notch-induced EMT is not a major contributor to renal fibrosis. While various experiments concluded that the NSP can be induced by hypoxia, the disparities in results of in vitro and in vivo experiments suggest that the NSP may not directly cause renal fibrosis. Therefore, more in vivo research should be conducted, with an emphasis on the molecular mechanisms of the NSP.

Abbreviations

CKD - Chronic kidney disease
CSL - CBF1 Suppressor of Hairless Lag-1
EMT - Epithelial-to-mesenchymal transition
FA model - Folic acid model
NECD - Notch extracellular domain
NICD - Notch intracellular domain
NSP - Notch signalling pathway
UUO - Unilateral ureteral obstruction

Introduction

Chronic kidney disease (CKD) refers to the gradual deterioration in the functioning of the kidney due to changes in its structure.[1] Since this disease is usually asymptomatic in the early stages, diagnosis typically does not occur until it has progressed to an advanced stage, making it difficult to treat effectively.[2]

The Notch signalling pathway (NSP) is highly conserved and is necessary for renal organogenesis, after which it is largely suppressed.[3] However, subsequent upregulation after kidney maturation has been associated with acute and chronic kidney damage.[3] This upregulation is facilitated by hypoxic conditions and results in renal fibrosis.[4] In essence, the NSP (**Figure 1**) involves the release of an intracellular component of a Notch receptor that serves to regulate transcription of Notch target genes.[5]

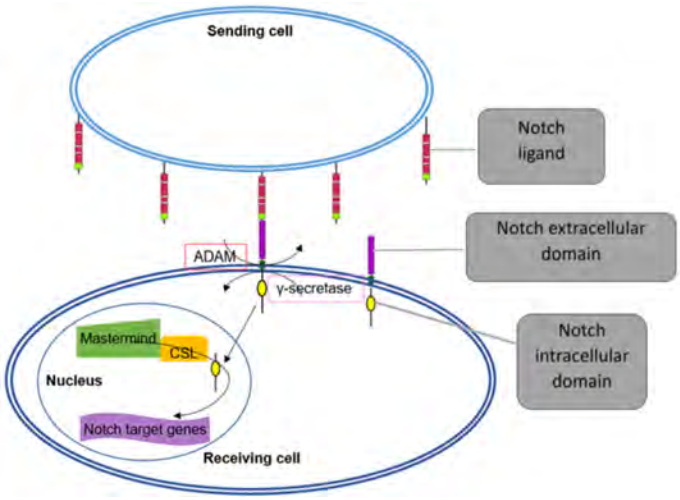


Figure 1. Diagram showing the Notch signalling pathway. Based on data from Mumm and Kopan (2000).[10]

The Notch receptor has two main components: the Notch extracellular domain (NECD) and Notch intracellular domain (NICD). The pathway

becomes activated when a Notch ligand from a sending cell binds to the NECD of a receiving cell. This promotes two proteolytic cleavages of the NECD and NICD, which are catalysed by an ADAM-family metalloprotease and γ-secretase, respectively.[1] The NICD becomes free within the cytosol of the receiving cell and enters the cell's nucleus, where it interacts with a DNA-binding protein known as CBF1 Suppressor of Hairless Lag-1 (CSL), its co-activator, Mastermind, and other transcription factors.[5] This process allows for Notch target genes to be transcribed.[1] Studying the intermediates of the NSP is hence important because it may signpost parameters that can be used to diagnose CKD and identify therapeutic targets.

While extensive research has been conducted on this topic, several uncertainties remain. The specific molecular mechanisms regarding hypoxia as a causative agent of renal fibrogenesis are not well elucidated. In particular, S2 cleavage remains an important aspect of further investigations since metalloproteases can be regulated by multiple external factors. Additionally, there is limited research about how the NSP operates under different temporal and spatial cellular resolutions. Temporal resolution refers to observations made over a period of time, while spatial resolution refers to observations made from a particular area or sample.

The primary aim of this review is to explore whether or not the NSP plays a role in hypoxia-induced renal fibrosis, by evaluating in vivo and in vitro experiments. The review will also consider some animal models that can be used to investigate this. Lastly, the interactions between the NSP and E-cadherin will also be briefly discussed.

Literature search

The sources utilised in this paper were acquired using the PubMed and Trip databases. Key words were extrapolated from the aim and included in the database searches. As such, the search term used was 'Notch AND hypoxia AND renal AND fibrosis'.

Filters were applied to refine the search to produce studies that have been published within the last twenty years. The titles and objectives of each study were then read to ascertain whether all the parameters of the search were discussed. Citation searches were also performed. Specifically, the article written by Sirin and Susztak, 2013, on the role of the NSP in the kidney was used to find primary research papers.[3] A flow diagram showing the identification process for eligible studies is shown in **Figure 2**.

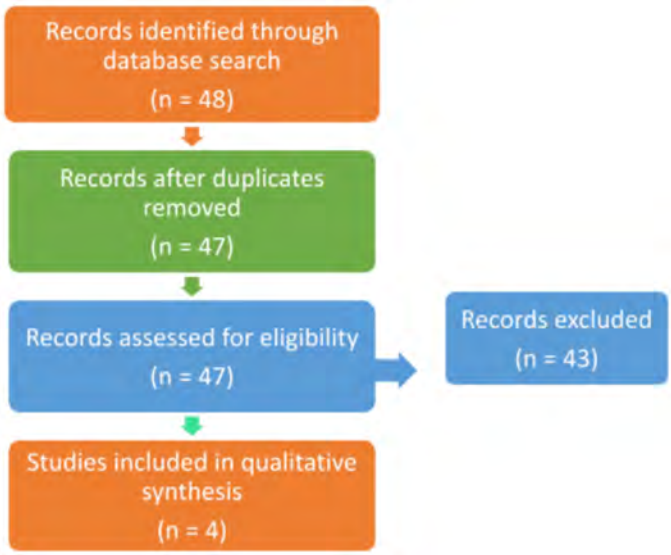


Figure 2. Diagram showing the identifi ation process for eligible studies.

Discussion

Animal models of renal fib osis Animal models are critical for biomedical research as they allow for the exploration of physiological functions and systemic interactions. Renal fibrosis can be studied using induced, spontaneous and in vitro models, amongst others. Specific to this review, two animal models will be discussed. The folic acid model (FA model) involves the administration of an injection of folic acid to mice. Folic acid precipitates in renal tubules, blocking the flow of luminal fluid through the nephrons and increasing the pressure within the tubules. This causes tubular epithelial damage and, consequently, acute renal failure, followed by renal fibrosis.

The unilateral ureteral obstruction (UUO) model involves the ligation of the ureter of mice. This prevents the flow of urine from the renal pelvis to the bladder and ultimately leads to acute kidney injury as a result of urea accumulation and pressure increase. Both models have limited temporal resolution but relatively high spatial resolution since immunohistochemistry is used to analyse the tissue.

How does hypoxia induce the NSP to cause renal fib osis? The NSP regulates hypoxia-induced renal fibrosis via several synergistic mechanisms.[4] Firstly, hypoxia triggers the epithelial Notch pathway by up-regulating the levels of NICD and expression of the ligand.[6] A study conducted by Bielesz *et al*. noted that after 1 and 7 days of administration of folic acid to mice, transcript levels of Notch receptors (Notch 1-3) and the ligand (Jag 1) increased at least two-fold (**Figure 3**).[7] The results of this study were further supported by in vitro experiments done by Sahlgren *et al*., which produced statistically significant results ($p<0.05$).[6] These observations highlight that hypoxia can both induce the NSP and amplify pre-existing Notch signalling.

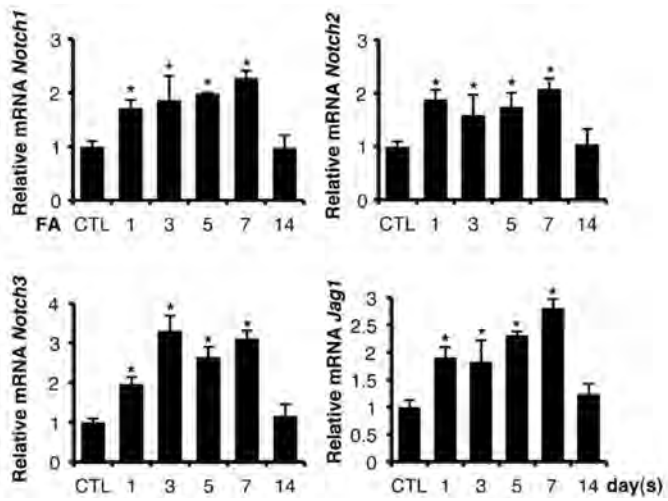


Figure 3. Graph showing the relative amounts of mRNA of different Notch receptors and a ligand. Graph showing the increase in transcript levels of the different Notch receptors (*Notch1*, *Notch2* and *Notch3*) and a Notch ligand (*Jag1*) after administration of folic acid (FA) in mice. CTL, control mice. Reprinted from Bielesz *et al*. (2010),[7] with permission from Elsevier.

Additionally, when the FA model was employed in conjunction with a γ-secretase inhibitor, the degree of fibrosis observed in histological samples was significantly less in comparison to the control.[7] This suggests that if the NSP is blocked, renal fibrogenesis decreases.

Sahlgren *et al*. performed experiments on cultured human cancerous ovarian cells and found that hypoxic conditions induced down-regulation of E-cadherin, up-regulation of fibronectin and N-cadherin, and morphological and molecular changes typical of epithelial-to-mesenchymal transition (EMT).[6] Fibronectin is an interstitial matrix component that precedes production of fibrillar collagens that eventually result in renal fibrosis.[8] E-cadherin is an adhesion molecule that contributes to epithelial cell behaviour and tissue formation;[8] its loss is often used as a marker of fibrosis. N-cadherin is expressed on mesenchymal cells.[9] Thus, the respective up-regulation and down-regulation of N-cadherin and E-cadherin promotes a mesenchymal phenotype for tissue, typical of renal fibrosis.

However, research done by Bielesz *et al*. showed that in vivo, Notch-induced EMT was not a major contributor to renal fibrosis.[7] This experiment was conducted using two animal models. In both cases, no decrease in mRNA or protein expression of Cadherin 1 was observed. No explanation was given for these results, though researchers referenced in vitro studies that obtained opposite findings. This highlights a gap in the literature that is limited by the external validity of in vitro studies.

Conclusions

In vitro experiments provide strong evidence to support that the NSP plays an important role in hypoxia-induced renal fibrosis. Both in vivo and in vitro studies reveal that hypoxia leads to an increase in the concentration of the NICD and the ligand.

With respect to EMT, the experiments conducted on cancerous ovarian cells and human renal tubular epithelial cells found that the NSP represses the expression of E-cadherin.

In conclusion, the NSP seems to play a role in hypoxia-induced renal fibrosis. However, fibrogenesis may not be a direct result of the pathway, but a result of interactions between the NICD and other mediators and transcription factors. As such, more in vivo research on the molecular knock-on effects of the NSP should be conducted to clarify this disparity, with a special focus on improving the temporal resolution of animal models used since CKD is a long-term illness. Finally, it is important to note that experiments involving murine species do not accurately represent the pathogenesis of CKD in a clinical setting due to anatomical and physiological differences between humans and mice.

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Review

Understanding the antenatal care experiences of women who have a learning disability in the UK

Eleanor Priestnall
Year 3, Medicine, University of Exeter
Email: Ep518@exeter.ac.uk

Abstract

This review highlights some of the key issues faced by women with learning disability (WWLD) during pregnancy and makes recommendations for improved practice. Experiences of maternity care among WWLD are mixed: some highlighted best practice but many reported barriers such as lack of reasonable adjustments, poor communication, inadequate training, poor attitudes and presumptive safeguarding decisions. However, the paucity of the existing research available limits transferability. Further qualitative research should be carried out to further understand experiences and ensure saturation of themes are found. Follow up with quantitative research is then required to understand how widespread these issues are.

Abbreviations

IPA - Interpretative phenomenological analysis
LD – Learning disability
WWLD - Women with learning disability

Introduction

Learning disability (LD) is described as a significantly impaired ability to understand new or complex information and learn new skills. Onset is before adulthood and can impact on the ability to cope independently.[1] The impact and limitations of LD vary but may lead to experiencing difficulty with everyday activities such as household tasks, socialising and managing money.[2] LD has been categorised by the World Health Organization's International Classification of Disease-11 (2018) with the associated prevalence being reported: mild (85%), moderate (10%), severe (3-4%) or profound (1-2%).[3]

The causes of a LD can be genetic, biological or environmental, or a combination thereof occurring before, during or after birth. Down syndrome is one of the most common causes, however in 30-50% of cases no specific cause is found.[4]

> *In England, it is estimated there are 297,033 people (0.5%) living with an LD,[5] however it is likely that numbers of people with LD is higher, with those having milder LD less likely to be identified by services.[6]*

Emerson *et al*. (2004), estimated the prevalence of LD in England to be 2.0% when measuring disability by intellectual and adaptive functioning, increasing to 2.5% when using IQ scores.[7,8]

Since the 1980s, people with LD have been supported to integrate into the community by moving away from hospitals and large institutions with the aim of improving quality of life. This transition has been largely positive with increased independent living, a recognition of the rights of individuals with LD and a shift in attitudes.[9,10] However, people with LD still face significant health inequalities, have worse health than the general population and face barriers in accessing health care.[11] Concerningly, women with LD (WWLD) are up to three times more likely to be a victim of physical abuse, sexual abuse or rape.[12] WWLD are often socially isolated with limited support networks and resources and may also be less able to follow health promotion advice.[13]

These risk factors result in WWLD having poorer pregnancy health:

they are at greater risk of severe pregnancy complications and poor birth outcomes, some of which can be reduced with early intervention.[14] Poorer outcomes include higher rates of pre-eclampsia, low birthweight and a higher proportion of babies admitted to neonatal intensive care.[15] It is therefore important to identify and understand experiences WWLD face and recognise failings in provision so that antenatal care can be improved, and inequalities reduced.

This article aims to discuss maternity care experiences for WWLD. It examines the women's perspectives in order to make recommendations for improved practice.

Methods

Search terms and Boolean operators were used to obtain relevant literature, as described in **Table 1** searching in the following databases: NICE Evidence Search, PubMed (Medline), TRIP and OVID (Medline). Filters were applied to find research in the last 10 years and in the English language only.

Table 1. Search terms and operators.

Search terms	Boolean operator
1. Learning disability* OR Intellectual disability* OR Developmental disability* OR Global developmental delay OR Down* syndrome OR William* syndrome[a]	AND
2. Maternity OR Maternal OR Antenatal OR Prenatal OR Pregnancy OR Expecting OR Midwi*	AND
3. Experience* OR Attitude* OR Knowledge OR Needs	

[a]Autism and Fragile X syndrome were not included in these search terms as a lower proportion of people with these conditions have an LD linked to their condition (only 1/3 of women and 1/2 of people for Fragile X syndrome and autism, respectively).[2]

Results were sorted according to search terms by order of relevance for each database. Titles and abstracts of the first 300 articles were then scanned in each database. Additional articles were found by searching reference lists of relevant papers. Further details of the search results can be found in **Figure 1**.

Women's perspectives

A systematic review by Homeyard *et al*. (2016) reviewed 16 papers of mixed methods and found significant gaps in the evidence base; however it highlighted some key issues and recommendations.[12] Women had difficulty finding out about their pregnancy and found antenatal information (often provided in text form) difficult to understand (including appointment letters and paper records). The research was dependable, using logical and auditable processes. Two reviewers independently assessed papers' eligibility, inclusion and exclusion criteria and quality. However, within the primary studies reported on, researchers did not consistently triangulate their findings among several researchers and data saturation was not always found, thus reducing our confidence in findings.[13] Additionally, Malouf *et al*. (2017) reported a lack of autonomy and disempowering practices by professionals to be common.[16]

Understanding information

The research found that during antenatal appointments, women regularly felt rushed.[16] The women reported being given standard, non-adapted information by their midwives, with some not given any at all. Those that did receive information in an easy-read format received it from other professionals.[16] Homeyard *et al*. (2016) suggest that

> *women with mild LD - who are at risk of not being identified by services - may be less likely to receive this support and additionally have difficulty keeping appointments.*

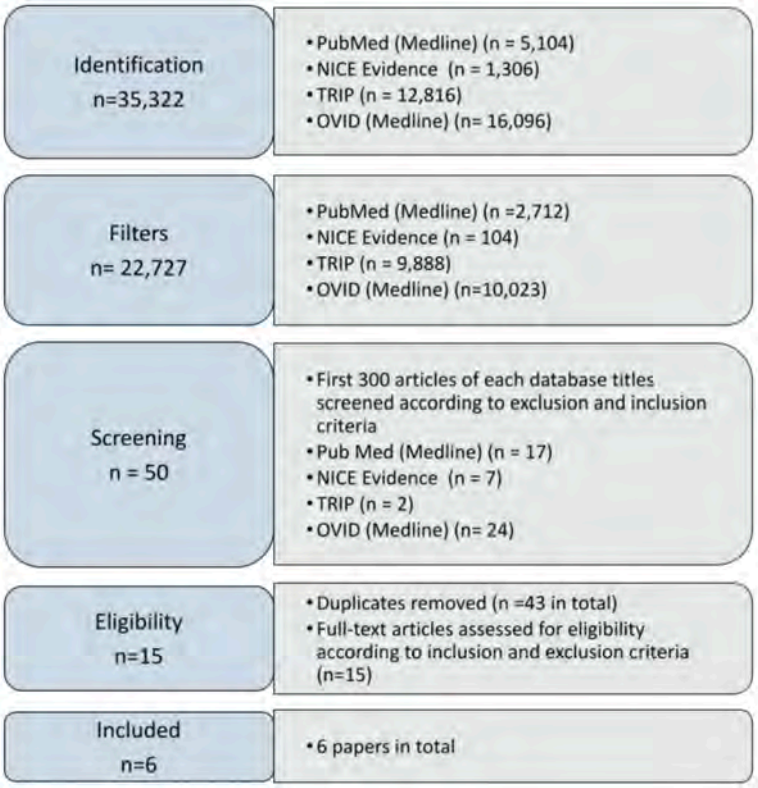
This cohort of women can often fall between services.[13] Findings were consistent across participants and saturation appeared to be reached despite women living in different areas of the UK, indicating reasonable adjustments are not provided as standard. This poses a concern as women could be denied information they need to be able to navigate their pregnancy successfully and learn important parenting skills.[16]

Malouf *et al*. (2017), carried out in depth semi-structured interviews exploring experiences of nine WWLD in the UK.[16] The authors found verbal communication during appointments was mixed, with some women giving positive feedback whilst others reported feeling ignored.[16] Discriminatory attitudes were accepted as being attributed to a lack of staff training highlighting how some WWLD accept the 'status quo' of not being provided with required adjustments/ supportive care.[16]

Malouf *et al*. (2017), used the analytical technique of 'interpretative phenomenological analysis' (IPA),[15] which aims to provide detailed examinations of personal lived experience, and requires fewer participants to find saturation of themes.[17] The sample demonstrated a fair representation of population disability severity but not of ethnicity, with only Caucasian women participating. Women were recruited by their support workers or midwives. However, this presumes active engagement with services and a higher level of communication as both are needed to offer study consent. The study may not therefore be representative. Furthermore, while the researchers did offer some reflexivity through a manual log, we know little about the interviewer and their background, which may have biased the interview process.[16]

These findings are reinforced by the results of a postal survey analysis on maternity care which was sent to over 50,000 women, three months after giving birth; 24,155 responded, of which 120 were WWLD.[18] However, it was not stated whether an easy read format was included therefore potentially biasing findings towards women with a milder LD. Redshaw *et al*. (2013) analysed the results from a disability perspective.[17] The analysis found a smaller proportion of WWLD compared to non-disabled women reported positive experiences: 66% vs. 84% were "always spoken to in a way they could understand", 63% vs. 74% were "involved in decisions about their care" and 58% vs. 73% were "always given help after contacting a midwife". Despite a smaller percentage of WWLD having positive views of aspects of their maternity care, 93% rated their overall antenatal care as good or better.[18]

Figure 1. Search strategy results.



Attitudes and autonomy

Women in the study by Malouf *et al*. (2017) had mixed views on how supported they felt by health and social care professionals.[15] Most reported midwives being helpful, friendly and respecting their right to make choices in their maternity care.[16] However, there were instances where health professionals, relatives and authorities restricted and sometimes violated women's autonomy to make their own decisions.[19] Some felt their social workers would support rather than scrutinise whilst others reported they had little encouragement, assumptions were made and that they had to "watch over (their) shoulder".[16] This caused some women to feel uncomfortable with disclosing their disability.[19]

Findings by Potvin *et al*. (2019) and Homeyard *et al*. (2016) described how professionals that knew the women provided long term support, facilitated better communication and had encouraging and non-judgemental attitudes.[13,20] Positive attitudes amongst medical staff were perceived to be attributed to 'help seeking behaviours', diagnosis, age and mental illness by WWLD. Jamieson *et al*. (2016) describe how fear or previous negative experiences can lead to reduced engagement and to women seeking help late in pregnancy.[20] This negatively impacts on support and safeguarding decisions made around their care and reinforces negative attitudes amongst professionals.[21]

Safeguarding decisions

Studies suggest the removal of children from parents with an LD is commonly as a result of prejudiced ideas around disability rather than the protection of the child or inability to parent.[22] Castell *et al*. (2016) reported that midwives desire to deliver the best care they could and demonstrated beliefs that WWLD had the right to be parents but required extra support.[23] Midwives felt support was available but not readily accessible. Midwives acknowledged that support can make a difference in the outcome of safeguarding however all assumed safeguarding procedures were an "inevitable" part of the pregnancy process for WWLD.[23] Many considered that the process could be done more sensitively, appropriately and with less pressure for WWLD.[24] There may have been some selection bias in the sample of midwives interviewed as they were self-selected through a poster campaign and were therefore more likely to have an interest in and motivation to improve the care of people with LD.[23]

Recommendations

Training emerged consistently from the literature as a priority. Studies recommend midwives receive training and supervision for working with and providing services for WWLD. Additionally, clinical opportunities should be provided for working with WWLD alongside teaching support for student midwives.[23] Training for General Practitioners should include: assessment and diagnosis; knowledge of associated conditions; how to make reasonable adjustments; adapting communication; skills for physical examination in non-compliant patients; service coordination; and involving patients in decision making.[21,23,24] In particular, making reasonable adjustments with respect to information giving, flexibility in services, consent, decision-making and assessment were highlighted. Homeyard *et al*. (2016) recommended reasonable adjustments should consider flexible and extended consultation times, communication aids, use of pictures, recording consultations, and flexibility in appointments with adequate time.[12] Jamieson *et al*. (2016) suggested women should be provided with information on the safeguarding process in advance.[20] This would reduce anxiety, stress and lessen surprise due to the unknown nature of the process of assessment.[13,21]

Professionals need to work together. It is recommended that local gap analysis concerning training, guidance and resources is conducted and LD midwife forums are created to address these gaps.[23] Additionally, independent advocates have been proposed,

who can work as 'facilitators' between parents and professionals to improve engagement, promote professional practice and model positive attitudes.[21,25]

In order to reduce fear and stigma around disclosing a pregnancy, Jamieson *et al*. (2016) recommend that services have proactive conversations with women about family planning.[21] Further suggestions include support networks developed for pregnant WWLD and routine antenatal screening for negative emotional states.[13]

Conclusion

The existing research is limited in breadth and depth: there are few papers capturing experiences of WWLD during pregnancy, and previous research has mostly focussed on others' perspectives on the matter.[19] Whilst this article provides a useful indicator of some of the issues WWLD may face during pregnancy, the paucity of the existing research limits transferability.

A number of issues were identified such as negative attitudes, lack of training and reasonable adjustments not being made. Easy read information was not being provided to women as standard, thus further increasing inequality faced by WWLD. Further qualitative research needs to be carried out across regions of the UK to encompass differences in antenatal services. In addition, a wider representation of ethnic groups should be included to further understand the experience of WWLD and to ensure saturation of themes are found. Quantitative research is then required to understand the prevalence of the issues and identify gaps regionally to put antenatal care support for WWLD into place.

Acknowledgments Thank you to Dr Guy Bradley Smith, University of Exeter, Exeter, UK, for facilitating the Learning Disabilities special study unit, for his support during the unit and feedback on my submitted essay.

Contribution statement The author has made substantial contributions to the conception of the work, drafted the article and gave the article final approval for inclusion in INSPIRE.

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Literature/Narrative Review

The role of human milk oligosaccharides, and mode of feeding and delivery in the development of necrotising enterocolitis in the neonatal gut

Kamal El-Badawi
Year 4, Medicine, University of Plymouth
Email: kamal.el-badawi@students.plymouth.ac.uk

Abstract

The aims of this review are to explore the role that human milk oligosaccharides (HMOs), mode of delivery and method of feeding play in the prevalence of necrotising enterocolitis (NEC). Articles from PRIMO and PubMed were reviewed, with inclusion and exclusion criteria added to identify papers specific to HMOs, Bifidobacteria, breast feeding or bottle feeding and the role of HMOs in the development of NEC. The review found that certain HMOs such as disialyllacto-*N*-tetraose (DSLNT) are protective against the development of NEC. HMOs are consumed by bacteria and metabolised via a fermentation pathway; this pathway is commonly used by Bifidobacteria species. Such findings allow for potential prebiotic formulas to be made, which can be used in infants not consuming breast milk. Studies show vaginally birthed neonates have greater proportions of bacteria which are known to inhibit pathogenic bacteria which cause NEC. However, the risk of NEC was only increased in C-sections of multiple pregnancies. Breastfed and bottle-fed neonates have different levels of beneficial bacteria such as Bifidobacteria, which are involved in outcompeting bacteria that can cause NEC, such as *Staphylococcus aureus*. The use of synthetic or natural HMOs, such as DSLNT, in formulas has shown promising results. These results aid in our understanding of the importance of breastfeeding and vaginal birth in preventing NEC development. Future work can be done to aid in prebiotic formulation and increase evidence identifying factors involved in the occurrence of NEC.

Abbreviations

ABC - ATP-binding cassette
ATP - Adenosine triphosphate
DSLNT - Disialyllacto-N-tetraose
F6PPK - Fructose-6-phosphoketolase
HMO - Human milk oligosaccharide
LNFP - Lacto-N-fucopentaose
LNnT - Lacto-N-neotetraose
LNT - Lacto-N-tetraose
NEC - Necrotising enterocolitis
TLR4 - Toll-like receptors

Introduction

Human milk oligosaccharides (HMOs) are complex carbohydrates that play an integral role in the development of the neonatal gut microbiome. HMOs can't be digested by infants yet are abundant in human breast milk.[1] The mode of feeding and delivery impacts the development of necrotising enterocolitis (NEC) in neonates.

HMOs act as immunomodulators, thus preventing disease propagation in the neonatal gut.[2] They also act as prebiotics by providing energy and nutrients necessary for commensal bacteria to proliferate and colonise the gut.[1] Energy is provided through HMO metabolism using the bifid shunt fermentation pathway, allowing

commensals to thrive. Certain HMOs such as disialyllacto-*N*-tetraose (DSLNT) have been shown to be protective against NEC.[3] Breastfed neonates consume these natural HMOs as opposed to synthetic oligosaccharides in formula, consumed by bottle-fed neonates.[4]

NEC is a disease where tissue lining the bowel becomes inflamed and eventually dies, leading to bowel perforation and contents of the bowel entering the abdominal cavity.[5] Bacteria leaking into the abdominal cavity can cause irritation and a local inflammatory response, or a systemic inflammatory response, known as sepsis, due to spread throughout the body via the blood.[6] NEC can be caused by pathogenic bacteria thriving in the gut lining, a lack of beneficial bacteria provided by the breast milk or potentially because commensals do not have enough nutrients to grow.

In comparison to bottle fed neonates, breastfed neonates have lower incidences of NEC.[7] The differences between NEC rates amongst neonates who have been breastfed, compared to those who have been bottle fed has been attributed to the absence of certain bacteria that metabolise HMOs. Further research is needed to explore the use of synthetic HMOs and their potential role in decreasing rates of NEC.

This review aims to explore the role of HMOs in the neonatal gut and their role in the development of NEC. Additionally, the effects of mode of delivery and feeding will be explored.

What are HMOs?

Breast milk is widely considered the best source of food for a new-born baby. It introduces essential nutrients into the body such as proteins, lipids, minerals, and carbohydrates as well as immunoglobins (IgA) and cytokines which are involved in fighting infection. A main component of breast milk is HMOs. These complex carbohydrates are present in breastmilk and act as prebiotics, encouraging the growth of good bacteria in the infant gut such as *Bifidobacterium infantis, Bacteroides fragilis* and *Bacteroides vulgatus*.[8,9] Over 100 different HMOs have been identified.[10] The most common being lacto-*N*-tetraose (LNT), lacto-*N*-neotetraose (LNnT) and 2'-fucosyllactose (2'FL) with a combined percentage 37.1% of all HMOs.[11]

All HMOs are made up of the same five basic monosaccharides: glucose (Glc), galactose (Gal), *N*-acetylglucosamine, fucose (Fuc) and sialic acid (Sia).[12] The structure of HMOs follows the same template, with there being a lactose group (made from galactose and glucose with a β1-4 bond, written as Galβ1-4Glc) bonded to either lacto-*N*-biose (type I structure) or *N*-acetyllactosamine (type II structure). **Figure 1a** shows the basic structure of HMOs. The addition of lacto-*N*-biose, shown in **Figure 1b**, elongates the molecule and causes the termination of the molecule. However, the addition of *N*-acetyllactosamine allows the addition of other monosaccharides, either fucose (fucosylation) or sialic acid (sialylation) to the molecule of lactose or the elongated lactose molecule (**Figure 1c** and **Figure 1d**, respectively)

Type I HMOs have a lacto-*N*-biose group (disaccharide with a Galβ1-3GlcNAc bond) bonded to lactose with a β1-3 bond, whereas type II HMOs have an N-acetyllactosamine group (disaccharide with Galβ1-4GlcNAc) bonded to lactose with a β1-6 bond.

In human breast milk, the concentration of type I HMOs, including LNT and LNFP I is higher than that of type II HMOs such as LNnT, LNFP III and DSLNT; this potentially sets humans apart from other mammals.[13] With greater knowledge regarding the structure of HMOs, research can be carried out in tailoring interventions for neonates to provide them with a healthy gut microbiome.

NEC

Multiple factors lead to the proliferation of a healthy gut microbiome, including mode of delivery and feeding.

NEC is a common gastrointestinal pathology in premature babies and carries a risk of causing neonatal sepsis if left untreated.[14] The pathophysiology of the disease involves the Toll-Like receptors (TLR4) present on enterocytes in the small and large bowels being activated by gram-negative bacteria (e.g. enterobacteria) which enter the infant gut following birth. The mucosal lining deteriorates, surrounding cells become inflamed and enterocytes undergo apoptosis. This causes a perforation in the bowel lining, allowing bacteria to enter the abdominal cavity and the blood stream, increasing the risk of peritonitis (inflammation of the peritoneum) and sepsis, respectively.[6] In addition, bacterial binding to TLR4 causes a reduced blood flow to enterocytes, leading to ischaemia and eventually necrosis.[5] Through a clear understanding of the pathophysiology of NEC, the role that mode of delivery and feeding have on its occurrence can be better understood. These factors therefore have potential for being utilised in the prevention of NEC.

DSLNT

A study carried out on rats identified HMOs as being protective against NEC, increasing the survival rate of neonatal rats from 73.1% to 95.0% compared to formula fed rats. In particular, an isomer of DSLNT was found to be protective against NEC.[3] However, this study was carried out in rats, therefore it cannot be assumed that the findings are applicable to humans. Another study in human infants found that those who had been breast-fed milk with lower levels of DSLNT developed NEC.[7] This supports the link between the lack of DSLNT and the development of NEC.

HMOs (including DSLNT) are not present in formula feeds given to infants. DSLNT promotes the growth of Bifidobacteria in the infant's gut, one of the most common bacterial species found in the gut.[15] Such bacteria inhibit the growth of pathogenic bacteria such as *Staphylococcus aureus* and *Clostridium perfringens*. Bifidobacteria does this by outcompeting the pathogenic bacteria for nutrients and preventing their adhesion to the epithelial cells lining the gut,[16] thus, ensuring pathogenic bacteria cannot colonise nor thrive in the gut.

Bifidoba teria and the bifid shu t pathway

Exclusive to the genus *Bifidobacterium* is the catabolic fermentation of HMOs by the phosphate phosphoketolase pathway (known as the bifid shunt pathway).[17] The enzyme fructose-6-phosphoketolase (F6PPK) is integral to the functioning of this pathway, and the final products of the process (lactic acid and acetate) are transported through the ABC transporters. The key product of this fermentative pathway is ATP. This pathway theoretically yields 2.5 moles of ATP for every 1 mole of glucose fermented, providing energy needed for bacterial growth and reproduction, eventually leading to bacteria colonising the infant gut.[18,19] 24 different strains of Bifidobacteria were analysed with regard to usage of the bifid shunt pathway, all of which tested positive for the presence of the enzyme F6PPK.[20] Therefore, the bifid shunt pathway may be the main method through which HMOs are metabolised.

Identifying the role of the F6PPK enzyme in the bifid shunt pathway allows prebiotics to be tailored to Bifidobacteria, thus preventing colonisation of pathogenic bacteria, such as *Staphylococcus aureus* which may cause NEC.[21] However, more studies on different Bifidobacteria strains are needed to determine whether the bifid shunt pathway is the most effective and main fermentation pathway involved in HMO metabolism.

A study by Hall *et al* from 1990 provides a different perspective on the argument.[22] The study was one of the earliest on the topic, therefore it gives a view of how the science has progressed over the years. Its conclusion is not consistent with that of updated studies from 2020 like that by Ma *et al*.[23]

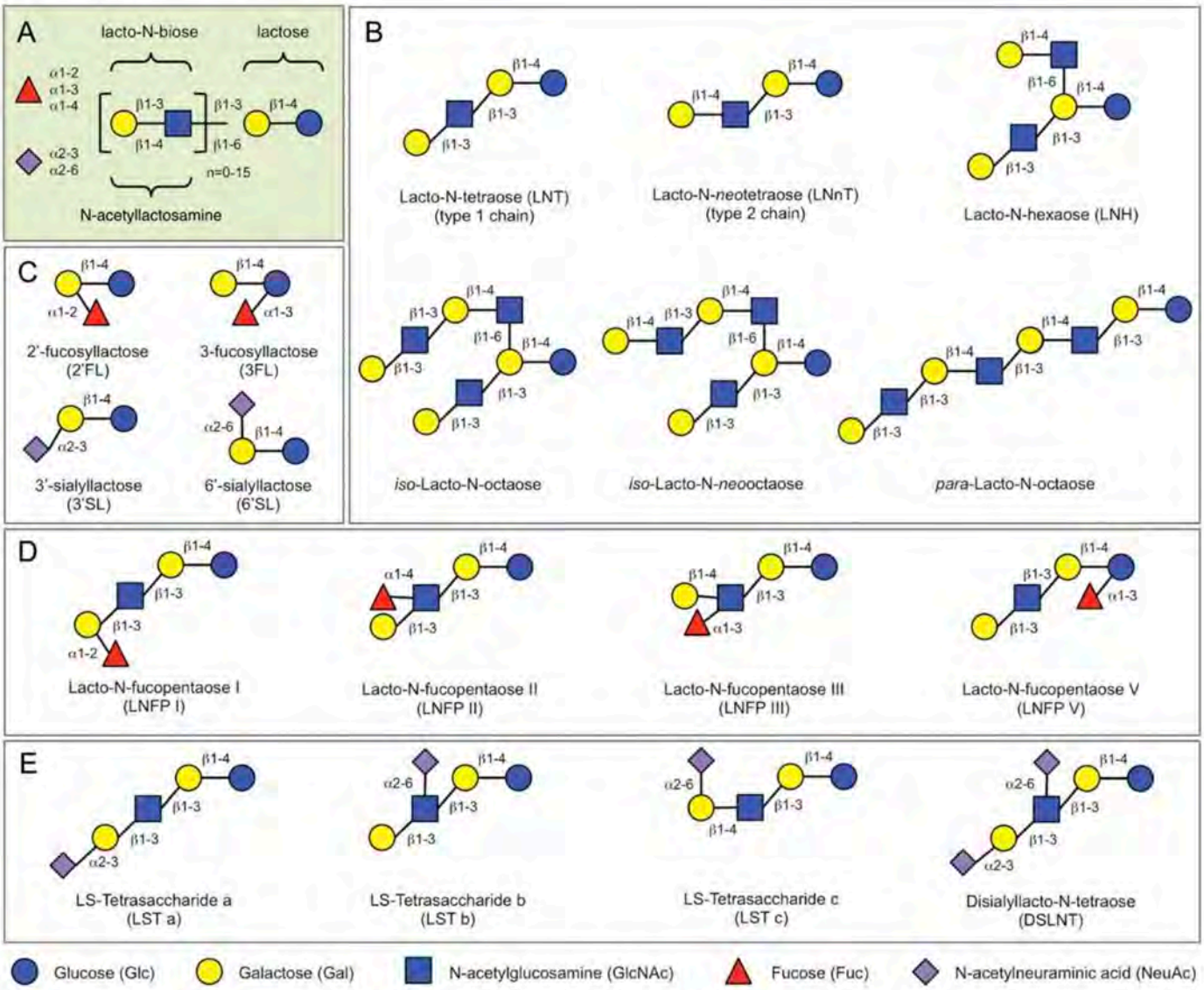

Figure 1. Different HMO structures. (a) Basic structure of an HMO. **(b)** Addition of lacto-*N*-biose to lactose. **(c)** Sialylation and fucosylation of lactose (by sialic acid and fucose, respectively). **(d)** Fucosylation of elongated lactose-forming multiple lacto-*N*-fucopentaose molecules. **(e)** Sialylation of elongated lactose (by N-acetylneuraminic acid, the most common sialic acid).[12] Reprinted from Bode (2012),[12] by permission of Oxford University Press.

Breast fed vs formula fed neonates

The consumption of breast milk or formula in infants has been linked to variation in the rates of NEC.[24] Breast fed infants have a 6- to 10-fold lower risk of developing NEC compared to formula-fed infants which is likely due to the absence of HMOs in formula.[7]

The difference between formula-fed and breastfed neonates commences when the baby takes its first breaths. Aerobic and facultative anaerobic bacteria, such as enterobacteria and streptococci species enter the gut and begin to colonise. These bacteria take up oxygen, allowing the natural proliferation of anaerobic bacteria, such as Bifidobacteria.[25]

Studies have shown Bifidobacteria has a much higher dominance in the guts of breast-fed neonates than in formula-fed neonates.[23] The gut microbiome of 4-week-old breast-fed neonates was found to be comprised of 69.96% *B. longum*, compared to 34.17% in formula fed infants.[16] These results show that bacteria unique to breast milk are introduced to the infant gut by breastfeeding. However, the results may not be representative of the general population, due to the study only being carried out on Korean infants, as there may be potential ethnic variations in *B. longum* populations. An opposing study carried out by Hall *et al* in the United Kingdom showed that there was no significant difference in the presence of Bifidobacteria between bottle-fed and breast-fed infants.[22]

The study by Lee *et al*.[16] using Korean infants had a smaller sample size compared to that used by Hall *et al*,[22] favouring the latter study due to the lower chance of including anomalous data. To combat this issue, the study by Sang *et al* should be repeated using a larger sample size, to accurately compare the two studies.

Many modern infant formulas contain supplementary plant oligosaccharides, which lead to less proliferation in Bifidobacteria colonies, compared to that of their mother's HMOs.[15] New-borns need these bacteria to improve their health, giving them the best opportunity to prevent the growth of bacteria which may cause infections or NEC.

Caesarean section vs vaginal birth

A Caesarean section (C-section) can either be elective or emergency. Elective C-sections are defined as procedures carried out "solely at the wish of the other, without any medical indication".[26] Studies have shown no difference in neonatal outcomes between elective C-section and vaginal deliveries.[27]

Bacteria are present on all parts of the skin and different modes of delivery expose different bacteria to the baby at the start of its life. Most of the differences can be normalised after consuming breast milk. Despite this, there may still be lifelong impacts of mode of delivery on the development of the gut microbiome.

Babies are exposed to different bacteria depending on if they are born via C-section (exposed to bacteria on the skin) or vaginally (exposed to bacteria in the vaginal canal). A study by Hällström *et al* suggested that there was a positive correlation between the mode of delivery and the onset of NEC.[28] With neonates who developed NEC, higher numbers of Enterococcus and *Candida albicans* were detected in stool samples. Compared to those delivered via C-section, vaginally birthed neonates were found to have an increased amount of Lactobacillus, which inhibit the growth of candida, protecting against NEC.[29] Supporting this is a study by Riskin *et al*, in which the risk of NEC was increased with C-sections, but only with multiple pregnancies.[30] However, the study by Riskin and colleagues was carried out using very-preterm (24-31 weeks gestational age) and very-low birth weight babies (<1500g), NEC is more likely in this demographic than in infants born at term or normal birth weight.

Another study, carried out by Son *et al* found no relationship between the mode of delivery and NEC development, contradicting the findings of Riskin *et al*.[31] Son *et al's* study was carried out using a larger population, reducing the likelihood of anomalous results. Considering both studies, there is an apparent increase in the risk of developing NEC for babies born by C-section in multiple pregnancies. However, due to the incongruence of conclusions, more research needs to be carried out to confirm an association between mode of delivery and onset of NEC.

Conclusion

HMOs are components of breast milk that are involved in the growth of beneficial bacteria and prevention of NEC. Studies identifying HMOs, such as DSLNT, as being protective against NEC were carried out on rats, therefore more research is needed into the role of DSLNT in the neonatal human gut microbiome. Plant saccharide supplementation has limited effect on NEC prevention and trying to mimic breast milk may show more potential in preventing NEC.

Regarding the mode of delivery and its effect on the prevalence of NEC, studies showed that babies born by C-section may be more likely to develop NEC. However, the study was carried out exclusively on pre-term infants, therefore, more studies must be carried out on term infants to confirm this.

Additionally, more research is needed to gain conclusive evidence regarding the effects of mode of delivery on rates of NEC before determining the need to reduce elective C-section rates. Once more research has been carried out, measures such as patient education of the risks of elective C-sections could be trialled, potentially reducing the prevalence of the practice and allowing infants to be exposed to vaginal bacteria.

Contribution statement The author declares that this is their own work. The author made substantial contributions to the conception or design of the work and drafted the work. The author has given final approval of the article to be included in Inspire.

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Research Highlights

A case of differing oligodontia in monozygotic twins

Asha Pandya-Sharpe
Dental Foundation Trainee, Dentistry, University of Bristol
Email: ap15966@alumni.bristol.ac.uk

Abstract

There are multiple aetiological factors for the developmental absence of teeth. Oligodontia is the congenital absence of six or more teeth and presents most commonly in association with a syndrome. Non-syndromic oligodontia may occur as a result of genetic factors, environmental factors or, most frequently, a combination of the two. This report presents a case of discordant, non-syndromic oligodontia in monozygotic male twins. The twins have a positive family history of developmentally absent teeth, suggesting a genetic cause for the condition, whilst the difference in clinical presentations between the twins may be explained by environmental and epigenetic factors. Awareness of the aetiology and recognition of a positive genealogy of hypodontia may play an important role in achieving early diagnosis and multidisciplinary treatment for patients with hypodontia. This may prevent the various functional and psychological difficulties associated with the condition.

Abbreviations

DPT – Dental panoramic tomograph
ISO – International Standards Organisation
MSX1 - Msh homeobox 1
PAX9 - Paired box 9

Introduction

Tooth agenesis refers to the failure of a tooth to form during development, and affects the general population at a prevalence rate of 1.6-6.9%. Females are more commonly affected than males.[1] Hypodontia refers to the agenesis of one to five teeth, excluding the third molars, whilst oligodontia is the congenital absence of six of more teeth and anodontia is the absence of all teeth.[2] The second tooth in each tooth series is most frequently missing, specifically the second premolars and upper lateral incisors. Moderate to severe levels of tooth agenesis, the absence of three or more teeth, can have significant aesthetic, psychological and functional consequences on patients of all ages.[3] Therefore, the primary aim when treating a patient with hypodontia is the development of a functional and aesthetic dentition. These goals may be met through a series of surgical, restorative, orthodontic, paediatric and prosthodontic work, which may take several years to complete.

Case report

This report defines a case of identical male twins with discordant oligodontia. Informed and valid consent was obtained from both twins to present and publish the findings in this case report.

At the age of 10, both twins were medically fit and well, and did not suffer from any systemic disorders. Intraoral examinations showed both twins were a class 2 division 2, a relationship where the maxillary jaw is positioned more anteriorly to the mandibular jaw than in an ideal occlusion, and where the upper anterior incisors were retroclined. They had severely displaced lower permanent lateral incisors, gingivitis and displayed signs of microdontia. Following referral for orthodontic treatment at the Great Ormond Street Hospital, UK, radiographs showed one twin to be missing teeth 15, 25, 34, 35, 44 and 45, whilst the other was missing teeth 15,13,12, 25, 35 and 45 **(Figure 1).** During the process of treatment to correct their displaced lower incisors with removable appliances, the twins were referred to the Hypodontia Clinic at a London teaching hospital where they received treatment from specialist dentists.

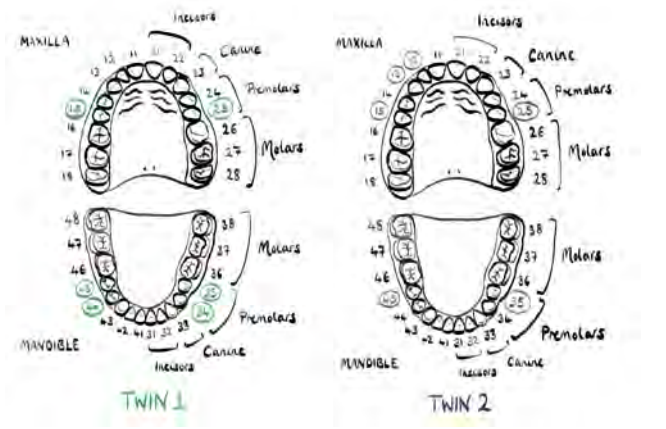

Figure 1. Labelled diagrammatic representation of the maxilla and mandibular arch, with teeth numbered according to the International Standards Organisation (ISO) numbering system. Green-coloured teeth are missing teeth from twin 1 and blue-coloured teeth are missing teeth from twin 2.

Further investigation, including a history from the patients' mother, revealed that the pregnancy and birth stages of the twins' lives were uneventful, but at 12 weeks old, one twin suffered from meningitis.

> *Investigation of the dental history from other family members revealed a positive history of moderate hypodontia in the twins' oldest brother.*

Following oral hygiene instruction and extensive orthodontic work to re-align, open and close spaces, at the age of 20, the twins had dental panoramic tomographs DPTs **(Figure 2)** and clinical photographs **(Figure 3)** taken prior to the commencement of the restorative aspect of their treatment.

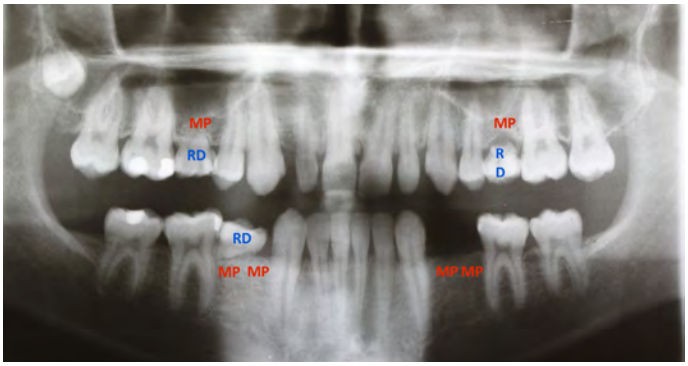

Figure 2. DPT of twin 1. The DPT of twin 1 shows multiple missing permanent (MP) teeth and three retained deciduous (RD) second molars.

Figure 3. Coloured clinical photograph of twin 1. The photograph shows retained deciduous (RD) teeth, spacing and upper microdont lateral (ML) incisors. Photo by Mr Jagdip Kalsi, Consultant in Restorative Dentistry at Croydon University Hospital (Surrey, UK), who has given permission for use.

Discussion

Tooth agenesis occurs due to failure of initiation within the dental lamina during odontogenesis and can be classified as being syndromic or non-syndromic. Syndromes that hypodontia have been associated with include ectodermal dysplasia and Down syndrome, among others.[2] Non-syndromic hypodontia and oligodontia are rare presentations that have been previously reported in twin studies.[4]

Hereditary genetic factors, epigenetics and various environmental conditions, including drugs, trauma and exposure to chemotherapy, have been found to be predisposing factors for non-syndromic hypodontia.[5] Hereditary hypodontia may be a result of autosomal dominant or recessive genetic traits. Mutations of numerous genes, particularly those encoding the paired box 9 (PAX9) and Msh homeobox 1 (MSX1) transcription factors, which are involved in the regulation of craniofacial development, have been found to be associated with missing premolar and molar units. Some studies have linked PAX9 to altered tooth size, specifically microdontia, which presents commonly in patients with hypodontia.[6]

Identical twins develop from one zygote and, therefore, share an almost identical set of genes.[7] Regarding the phenotypic differences that are notable between identical twins, evaluation of twin studies suggest interactions between genes, common environmental variance and unique environmental variance to be the causes.[8] Epigenetics refers to the variation in phenotype that occurs as a result of gene expression modification as opposed to a change in DNA. This may occur in response to an environmental assault, hormones, inflammation or stochasticity.[9] A single mutation in developmental regulatory genes, or an environmental insult, possibly meningitis in twin 1 in this particular case, may affect the balance between activating and inhibiting genes involved in odontogenesis. The macroscopic consequences are alterations in tooth eruption patterns, tooth structure or tooth formation.[10]

Severe hypodontia can have a significant impact on quality of life.[11]

> *Primary aims when treating a patient with hypodontia are to improve aesthetics, maintain or increase vertical dimension and enhance dental function to improve phonetics and mastication.*

Treatment of patients with hypodontia can prove to be complicated, requiring a multidisciplinary approach including involvement from paediatric dentists, orthodontists, restorative specialists and implantologists. **Figure 4** and **Figure 5** show the stages in the placement of dental implants following restorative planning and the orthodontic movement of teeth. Delayed treatment referral has been found to have 'social and educational' implications for patients with hypodontia,[12] and studies have shown that older patients with a better understanding of their condition are more concerned about their appearance.[3] This has, in turn, had a greater impact on their psychological welfare than younger patients.

Figure 4. Coloured clinical photograph showing placement of dental implant and abutment as further treatment carried out by the multidisciplinary team. Photo by Mr Jagdip Kalsi (Croydon University Hospital, Surrey, UK), who has given permission for use.

Figure 5. Coloured clinical photograph of twin 1 showing a final implant restoration. Implant restoration was used to replace teeth 34, 35, 44 and 45, with two large molar shaped implant crown prosthesis. Photo by Mr Jagdip Kalsi (Croydon University Hospital, Surrey, UK), who has given permission for use.

Conclusion and clinical signifi ance

The genetic and environmental factors that play a role in the aetiology of non-syndromic oligodontia have been reported in several case reports.[13] Twins share most of their genetic variants which accounts for their similarity in presentation. Despite this, differences in medical conditions, levels of obesity, or dental anomalies present in many monozygotic twin studies. These studies show phenotypic differences between identical twins to be influenced by environmental and epigenetic factors.[9] Although rare, dentists should be aware of the various syndromic and non-syndromic causes for oligodontia. They should take into consideration the significance that a positive family history of hypodontia has on the chance of subsequent family members inheriting the condition, as early referral and successful treatment may result in fewer psychosocial and functional implications for the patient.

Acknowledgements I would like to offer my special thanks to Mr Jagdip S. Kalsi BDS MSc MFDS MJDF MRD FDSRCS Consultant in Restorative Dentistry at Croydon University Hospital (Surrey, UK) who undertook the restorative treatment of Twin 1 and provided me with the patient photographs and DPT for use in this article. I would also like to thank Dr James Puryer BDS DPDS MFDS RCS(Eng) FDFTEd MSc FHEA Senior Clinical Lecturer in Restorative Dentistry and Assessment Lead at the University of Bristol (Bristol, UK) who helped with the editing and proof-reading process of this piece of work.

Funding This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Contribution Statement The author meets the following criteria: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Research Highlights

Expected functional loss and factors affecting recovery in patients with traumatic peripheral nerve injury in the upper limb

Harris Mangal
Year 2, Medicine, University of Exeter
Email: hm549@exeter.ac.uk

Abstract

Traumatic peripheral nerve injuries are nerve injuries that occur in the upper and lower extremities of the body initiating a variety of neurological symptoms. These range from motor to sensory deficits in the affected limb based on the severity and type of nerve injured. While there is increasing knowledge of the mechanisms of injury and regeneration, treatment is suboptimal resulting in major incapacities in the most active populations of society. Studies have purported many factors that can affect the recovery of a nerve and ameliorate functional outcomes. However, given the complexity of nerve anatomy and topography prognosis is highly unpredictable. This paper aims to review the effects of the type of nerve injured, age and gender, and how time between nerve injury and repair affects functional recovery. The case study format provides essential insight into factors that need to be considered in a clinical setting by physicians in order to produce better outcomes for patients. Furthermore, the case study concludes that the aforementioned factors have a significant impact on nerve recovery and functional outcomes in patients. In general, younger female patients with shorter axonal lengths, less atrophy following trauma and with the endoneurium intact had a better prognosis. Furthermore, surgical delays reduced good neurological recovery. Expected functional loss and factors affecting peripheral nerve recovery are multifaceted and the need for a meta-analysis of many other factors in conjunction to those mentioned is crucial.

Abbreviations

BDNF - Brain-derived neurotrophic factor
TPNI - Traumatic peripheral nerve injury
VEGF - Vascular endothelial growth factor

Introduction

Traumatic peripheral nerve injuries (TPNI) are common, especially in injuries affecting the upper limb. The nature of the injury is usually attributed to motor vehicle accidents, violence, sporting and recreational injuries, as well as iatrogenic injury during surgery. In addition to the posttraumatic stress a patient endures, if a length of nerve is damaged, functional recovery is substantially affected. Patients can be left severely debilitated with chronic neuropathic pain and neurological deficits, jeopardising their ability to work and return to a normal life.[1]

This study will aim to discuss how the significance of the type of nerve trauma, age and gender, and the time between injury and nerve repair impact functional recovery providing essential consideration for physicians. The article will revolve around a case-based analysis of a patient with peripheral upper limb nerve trauma at the Princess Elizabeth Orthopaedic Centre in Exeter. The patient provided consent for use of their data (for patient details, see **Text box: Patient case summary**).

Patient case summary

Initials: CA

Age: 21

Gender: Male

Operation: Exploration right elbow wounds and repair ulnar nerve

History: Fall onto broken tiles 4 days ago

Findings:

- Multiple ragged wounds over extensor and medial aspect of elbow
- 50% division of ulnar nerve at medial epicondyle with motor to intrinsic bundle and sensory to hand bundle affected
- Multiple ceramic fragments in wound including within ulnar nerve

Discussion

Clinically, outcomes of peripheral nerve injuries have been poor even with the intervention of the most experienced surgeon. While there have been little changes in surgical repair techniques over the past decade, other factors may impact functional loss to a greater extent. Some of these factors include: age, gender, type of trauma, repair time, adjuvant therapy, duration of follow ups and lengths of nerve grafts. However, independent predictors of successful outcomes can be hard to identify conclusively.

Nature and extent of nerve trauma Patient CA explained, *"I fell into some broken tiles four days ago and my elbow was hurt really bad. I couldn't move my arm or my fingers because of the unbearable pain and it was bleeding a lot. Even now, after surgery, I still have pain that keeps me up at night but I am taking Amitriptyline for it. As most university lectures are online, I feel I can manage the pain and I am now able to make a fist. I do occasionally get pins and needles and shooting pain in my ring and long fingers and it affects my ability to type and write."*

The nature and extent of nerve trauma plays an important role in neurological recovery. Typically, a nerve trauma may be categorised into tidy and untidy wounds, whereby tidy wounds (glass, knife and other sharp instruments) contain no devitalised tissue and have a better prognosis than untidy wounds (shrapnel, bullets, contamination).[2] Tidy wounds involve less damage to longer lengths of nerve, requiring less excision and hence recovery is quicker and functional loss is minimal.[2] Untidy wounds can present with loss of nerve vascularisation, especially when axons are inhibited from renewing in areas where trauma has left the distal nerve non-vascularised.[2] Patient CA experienced an untidy wound with penetration of ceramics fragments into his ulnar nerve causing motor deficits to the intrinsic muscles of his hand and sensory loss to his hand bundle. The injury caused a 50% division of the ulnar nerve at the medial epicondyle resulting in these functional losses.

In the case of patient CA, he had weakness in his intrinsic muscles and paraesthesia that improved very slightly postoperatively, along with his ongoing neuropathic pain. This indicates that he had a neurotmesis (**Table 1**). It is crucial that the type of nerve injury is identified as it acts as a strong indicator of prognosis and rehabilitation time.

Table 1. The types of nerve trauma as classified by Seddon (1954)[3] during his World War 2 experiences of nerve injuries.[3-5]

Type of nerve injury	Layers of nerve involved	Is the axon involved?	Symptoms expected
Neuropraxia	Damage to myelin sheath	No	Transient functional loss
Axonotmesis (2nd degree)	Axon severed, myelin degeneration, endoneurium intact	Yes	Complete denervation. Excellent prospect for recovery
Axonotmesis (3rd degree)	Axon division, endoneurial tube discontinuity, perineurium and fascicular bundles preserved	Yes	Complete denervation
Axonotmesis (4th degree)	No axonal continuity, no endoneurial tube continuity, no perineurium and fascicular continuity, epineurium intact	Yes	Complete denervation
Neurotmesis	Entire nerve trunk affected	Yes	Complete functional loss and denervation without surgical intervention

When a TPNI presents proximal to the site of injury, recovery of the nerve and functionality is usually poor. In a study of 2210 gunshot wound patients with peripheral nerve injuries, like CA, poor muscle strength levels (≤M2) preoperatively were found in 86.73% of the 407 ulnar nerve injuries (**Table 2**). Median, tibial and peroneal nerves followed in strength levels respectively.[6] Useful good muscle power recovery (≥M3), postoperatively, was second to last for ulnar nerves (56.76%) following the brachial plexus (49.01%; **Table 2**). Poor sensory levels (≤S2), preoperatively, were second highest for ulnar nerves (94.1%) after radial nerves (94.51%; **Table 3**). Postoperatively, useful good sensory recovery (≥S3) was second to last for ulnar nerves at 64.86% (**Table 3**).[6]

> *Therefore, ulnar nerve injury was associated with poor muscle strength and poor sensation levels pre-operatively, with poor post-operative outcomes for muscle strength and sensation, in comparison to most other nerve injury types.*

Despite the study involving high-velocity and high-level injuries to the ulnar nerve, the findings corroborate the functional outcomes the patient spoke about. Functional recovery depends on regeneration of nerve fibres from the site of the injury to the distal site of innervation. Therefore, a proximal nerve injury at the medial epicondyle

for CA will take longer to recuperate with a risk of neuronal necrosis at the site of the injury affecting functional recovery.[7] Although, this is highly dependent on the type of nerve trauma, as a neuropraxia would have resulted in less motor and sensory dysfunction.

Table 2. Muscle strength grading. Adapted grading of muscle strength for peripheral nerve injuries caused by gunshot wounds in adults.[6]

Grade of muscle strength	Description of response elicited
M0	No contraction
M1	Minimal muscle contraction
M2	Perceptible contraction without gravity
M3	Active movement against gravity
M4	Active movement against resistance performing all independent and synergistic movements
M5	Normal strength and complete recovery

Table 3. Sensory grading. Adapted grading of sensory function for peripheral nerve injuries caused by gunshot wounds in adults.[6]

Grade of sensory strength	Description of response elicited
S0	No response to any pressure stimulus
S1	Testing gives hyperesthesia, paraesthesia or pain
S2	Overresponse to sensory stimuli; sensory response slow but can grip adequately
S3	Some overresponse to sensory stimuli; response to touch and pin pressure
S4	Abnormal localised response to sensory stimuli with no overresponse
S5	Normal response to any sensory stimulus in all body fields

Consequently, the type of nerve trauma is an important factor in the recovery of nerves following injury and functional loss can vary according to the extent of the nerve injury, especially if it is an untidy wound involving Wallerian degeneration. From a patient perspective, the extent of the nerve injury can be both alarming and life changing, such as hindering CA in his university studies and daily activities (for patient remarks, see **Text box: Patient comments**). So this is an important consideration for both patients and physicians.

Patient comments

"I was told by the therapists not to play rugby until I recovered and that I would not be able to sense anything on inside of my palm. They said I could get serious injuries if I was not careful and that I have to wait longer until I can feel again. But I am finding that moving my fingers is becoming better day by day."

Age and gender Studies clearly support that younger patients are more likely to have better outcomes and regain functionality following peripheral nerve injury compared to elderly patients.[8,9] In a univariate analysis by He *et al.*,[10] for every increase in age by a year the odds ratio for a good to excellent recovery in sensory functionality following repair was 0.98 (95% CI: 0.96-0.99, P<0.05). The odds ratios for motor recovery was 0.97 (95% CI, 0.96-0.99, P<0.05). Age is therefore an important consideration, especially when evaluating whether a patient may be eligible for surgery and how many potential quality-adjusted life years this would give them.

> *Younger patients may show better outcomes due to shorter axonal lengths, more efficient regenerative abilities and less atrophy following trauma.*

However, other studies allude to the fact that age may be related to declining expression of vascular endothelial growth factors (VEGFs), which are required for axon regeneration.[11] This is central to the fact that endoneurial vasculature is needed for angiogenesis and the outgrowth of axons from the proximal nerve stump.[12] In a patient, such as CA, age may have ameliorated poorer outcomes due to better vascularisation but vascular features may differ from person to person despite age differences. Moreover, encouraging vascularisation in patients older than CA may yield better neurological recovery, particularly if there is ischaemia in the damaged area.

Gender may be a factor that is overlooked following nerve injuries and the lack of studies regarding gender and recovery substantiates this. Univariate analyses following nerve repair of mixed nerve injuries in females versus males showed that the odds ratio was 2.19 (95% CI: 1.06-4.52, P<0.05) for motor recovery and 1.53 (95% CI: 0.82-2.85, P<0.05) for sensory recovery.[10] As suggested from this study,

> *females have better outcomes in terms of functionality (motor and sensory) when compared to their male counterparts*

but this does not warrant a causal link between gender and recovery. Various animal studies have presented different results with regards to how gender may affect recovery making it difficult to come to conclusions. Androgens have been found to play a vital role in axon regeneration, causing the expression of brain-derived neurotrophic factor (BDNF) via different mechanisms in males and females.[13,14] However, the use of hormones to increase recovery of damaged peripheral nerves requires more studies. In addition, expected functional loss may be due to factors that were not considered in the previous studies such as fewer women partaking in labour intensive activities and female engagement with post-operative therapy differing from male engagement.

Therefore, age and gender are pivotal factors in nerve recovery and it is important for a physician to consider these variables in assessing functional loss. In the case of CA, a young 21-year-old male, sensory function remained impaired 3 weeks after surgical intervention and follow ups, but motor function of intrinsic muscles improved considerably (for patient remarks, see **Text box: Patient comments**).

> *In a clinical setting, knowing the age of the patient may provide a physician with a more informed choice as to what surgical interventions can be used, whereas gender may provide an indication into better postoperative rehabilitation.*

All in all, this will reduce expected functional losses and aid recovery.

Time between injury and nerve repair There is a strong link between the time taken to repair a nerve and functional recovery, with various studies supporting this. A study of 242 repairs of radial nerves found that 49% of the repairs that took place within 14 days of the injury achieved a good result, and only 28% of the later repairs had similar results. Good results consisted of proximal muscles having a grade of M5 or M4 (powerful elbow extension) and distal muscles having a grade of M3 (wrist extension against gravity).[2] Furthermore, the same study also showed that when surgery was delayed, good neurological recovery falls to 30% and fails for 42% of patients. Therefore, direct anastomoses of distal nerve stumps or even a stage of repair is required early on to improve prognosis. Leaving the injury for more than 6 months can reduce recovery leading to outstanding neurological deficits.[15] Repairs left for more than 10 months showed no functional recovery postoperatively due to the predominant atrophy of terminal receptors and scarring of distal nerve endings.[16] Given that nerve regeneration takes place at a rate of 1mm/day it is crucial that there is no delay in surgical intervention to ensure good outcomes.[17]

Hence, repair time is a vital factor in the recovery of nerves and so delaying it, particularly after 6 months, will result in significant sensory and motor dysfunction. Even though ulnar nerve repairs tend to have poor outcomes, CA managed to achieve a substantial recovery due to the immediate surgical response. CA's success may lie in the careful management and triaging of his case, which can be used for other patients with more traumatic injuries.

Conclusion This case-based analysis of expected functional loss and factors affecting recovery of peripheral upper limb nerves has shown the gravity that age, gender, type of nerve trauma and repair time can have on prognosis. Patient voice has been incorporated throughout this article, giving first-hand outcomes of patient experiences and providing essential considerations for physicians. It is difficult to maintain homogeneity of results due to the disparity in types of trauma. Furthermore, small samples sizes and a lack of statistical tests and randomised controlled trials may have caused limitations to this article. Overall, expected functional loss and factors affecting peripheral nerve recovery are multifaceted and the need for a meta-analysis of other factors, including those mentioned, is key.

Acknowledgements I would like to thank all the Consultants and staff at the Royal Devon and Exeter Plastic Surgery and Orthopaedics department (Exeter, UK). Special thanks to Yeru Chin (CST1, Plastic Surgery, Royal Devon & Exeter Hospital, Exeter, UK) for organising the placements and Nalin Nagrath (StR, Plastic Surgery, Royal Devon & Exeter Hospital, Exeter, UK), as well as the University of Exeter. Further thanks to the peer reviewers and editors who reviewed this article for their highly beneficial suggestions and feedback.

Contribution statement The author made substantial contributions to the design and analysis of the article. This included drafting and editing the article based on peer reviewers' and editors' comments in order to produce the final copy for approval by the Inspire student journal team. The author gave final approval for the article to be included in Inspire.

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Research Highlights

Using machine learning for rapid intracranial haemorrhage segmentation on axial computed tomography slices

Frederick Renyard
Year 3, Medicine, University of Bristol
Email: tw18869@bristol.ac.uk

Abstract

Introduction This study aimed to explore ways in which machine learning can be used for rapid segmentation and explainable classification of intracranial haemorrhage and discusses other potential implementations of the technology.

Methods An existing architecture was applied to a dataset of axial, brain-window slices of haemorrhagic and non-haemorrhagic scans, with radiologist masks over areas of diagnosed haemorrhage.

Results As a classifier, the model used in this study achieved an area under a precision-recall curve value of 0.93 (95% CI: 0.925, 0.935) and a maximum F1 score of 0.875 (95% CI: 0.817, 0.933) on the test dataset. When used for segmentation, the model achieved a maximum correlation coefficient of 0.80 ($p < 0.001$). When used to predict haemorrhage area, the intersection over union score was 0.64 (95% CI: 67.5, 75.7).

Conclusion The model used in this study quickly produces inferences, which is suited to real-time imaging modalities, such as ultrasound. However, more training data is required to improve the model, and external validation should be conducted to confirm the results.

Abbreviations

AUC - Area under the curve
CT - Computed tomography
IoU - Intersection over Union
ROC - Receiver-operator characteristic

Introduction

Intracranial haemorrhage is both a life-threatening and time-sensitive diagnosis, with one year mortality ranging between 51% and 65% and half of deaths occurring within two days.[1] Computed tomography (CT) scans are done routinely in trauma and stroke settings, in which time to diagnosis is crucial. The use of machine learning has been shown to reduce reporting time in trauma and stroke clinical settings, along with reducing length of stay in the Emergency Department.[2]

Machine learning is the use of statistical inference algorithms to predict diagnoses. The technology could provide an accessible method for rapidly extracting interpretations of data to improve patient outcomes.[2] The aim of this study was to develop an algorithm for imaging analysis via a method known as semantic segmentation, whereby an algorithm assigns a value to each part of an image according to how likely the part belongs to a class, such as "haemorrhage" or "fracture". These inferences are learnt from a dataset of pre-segmented images[3] (see **Figure 1**). This technique is already being used in biomedical sciences, from assigning cell types in microscopy to assisting brain mapping in neuroscience.[4,5]

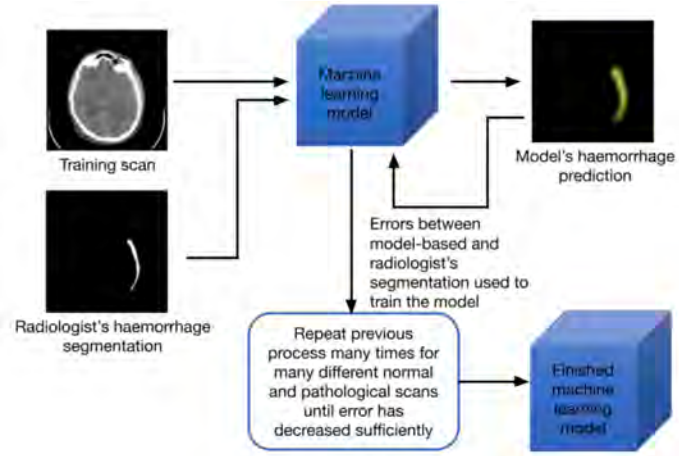

Figure 1. Machine-based learning. General overview of how a machine learning model for semantic segmentation is trained to produce a functional model. Scan images from Hssayeni (2019).[6]

Methods

A technical description of the results can be found in the GitHub repository: https://github.com/freddie-renyard/CT-Segmentation-UNet. The repository includes information on all code used in data pre-processing, model design, and post-training analysis, along with the final model and a full set of results as graphs.

The model was developed using Google's TensorFlow library. The structure of the model was based on an existing architecture known as U-Net, which was developed for use in biomedical applications due to its ability to learn from small datasets. The architecture is small, requiring less computational resources to run the model.[4]

The dataset was sourced from the data science website Kaggle (https://www.kaggle.com/vbookshelf/computed-tomography-ct-images), being made publicly available by Murtadha Hssayeni. The images were collected over a 7 month period at Al Hilla Teaching Hospital, Iraq, as part of a study by Hssayeni.[6] Ethical approval was granted for the study by the Iraqi Ministry of Health and all data was completely anonymised.[6]

The dataset contains the bone and brain windows of around 30 slices of axial CT scans of 82 patients, totalling 2500 images for each window. A description of patient demographics can be found in **Table 1**. The scans contain different types of intracranial haemorrhage, as well as non-pathological images (see **Table 2**). They also include segmentations of areas where there is intracranial haemorrhage present in each slide, which are annotated by radiologists.

Table 1. Patient demographics.

Number of patients	82
Mean age (±standard deviation)	27.84 ± 19.52
Maximum age	72 years
Minimum age	1.7 weeks
Male:female ratio	1.28:1

Table 2. Frequency of different haemorrhage types in the dataset.

Haemorrhage type	Percentage of patients with diagnosis
No haemorrhage	56.1%
Intraventricular	6.1%
Intraparenchymal	19.5%
Subarachnoid	8.5%
Epidural	25.6%
Subdural	4.9%
Fractures present	26.8%

Before training the model, the data was pre-processed and sorted into pathological and non-pathological classes. The brain windows were used for model training. Since testing data was not given in the dataset, four full cases (amounting to 127 images) were withheld from the training dataset to serve as validation data and testing data, enabling the model to be evaluated with data that it had not been trained on.

In order to expand the small dataset, extensive data augmentation was used. These were all biologically plausible modifications.[7] The techniques used were:

1. Horizontal flipping: reverses left and right
2. Rotation: randomly rotates the image by up to 40 degrees, which frequently occurs due to suboptimal patient positioning during imaging
3. Shearing: randomly shears the image
4. Zooming: randomly zooms the image, simulating different patient sizes or scan setups
5. Brightness: randomly changes brightness, simulating different scan settings
6. Elastic deformation: randomly deforms the image, simulates patient tissue differences (note, this has been used to train more accurate models in radiological settings due to the biologically plausible method of deformation).[7]

See **Figure 2** for examples of scans before and after the techniques have been applied.

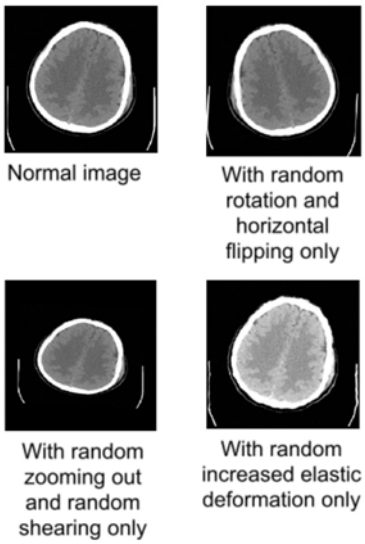

Figure 2. An example of the data augmentation techniques used to augment the relatively small dataset used in this study. Note: the intensity of the elastic deformation presented was twice what was used during training. Scan image from Hssayeni (2019).[6]

The data in the dataset was unbalanced, consisting of 2,182 normal images against 318 pathological slides. The type of network used (convolutional neural network) has been shown to produce more accurate models when trained on a dataset that has been made to be balanced by duplicating images.[8] Thus, the dataset was balanced out via pathological slide duplication, bringing the number of pathological images to 2,024.

The model's architecture was created using code from an existing implementation by the GitHub user 'nikhilroxtomar';[9] the code for model training and data pre-processing was written separately. The model is trained by inputting image data along with annotations made by radiologists. Parameters of the network are modified until maximal performance metrics are reached. The model contains 1,962,337 modifiable parameters.

For training, the images underwent data augmentation, as detailed above, increasing the number of training images used per epoch to

5000. The validation dataset consisted of 127 images from 4 random cases and was used to evaluate the model at the end of each epoch of training data. To allow evaluation of the final model on the validation data, the model did not learn from this validation data. This process was repeated 144 times (144 epochs of training), with the images being used in batches of 16. Training took approximately 18 hours on an NVIDIA® GeForce® RTX 2070 SUPER®. The model was saved every 5 epochs to allow for the evaluation of successive models; this ensured that overfitting of the model to the data did not occur.[10] The error during training on both data partitions is shown in **Figure 3**. Unexpectedly, the error was greater for the training data than the validation data. This is likely to be attributed to the fact that extensive data augmentation had been applied to the training data, but no augmentation was applied to the validation data, as would be the case if the model were to be evaluated using clinical data.

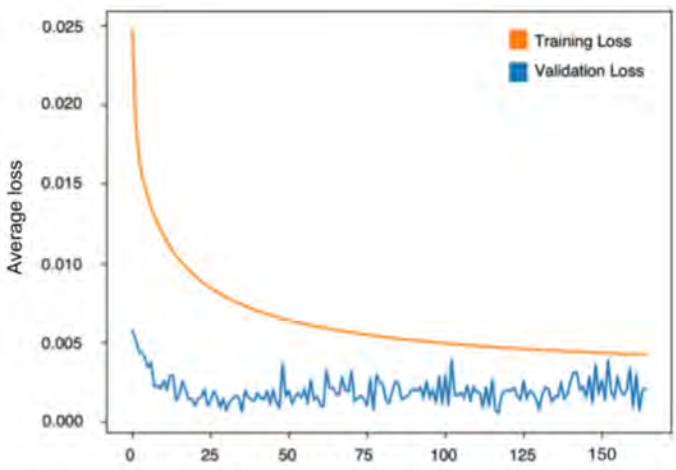

Figure 3. A graph of the mean loss of the model during each epoch (training loss) or with the validation data (validation loss).

Final evaluation of the model was performed on the four cases that were withheld from the original dataset (i.e. data that it had been trained on). The model was evaluated for its ability to classify scans as haemorrhagic and normal, and for its ability to segment the pixels into haemorrhagic and normal classes. The testing data included both normal scans and scans with haemorrhages.

Results

Classification The main metric used to evaluate the model's performance as a classifier was a precision-recall curve. The model's output was haemorrhage probabilities for each pixel. The mean of all predictions across each image in the test dataset was calculated and processed using a threshold to obtain a binary classification. Different precision and recall values were produced depending on where the threshold was set (see **Figure 4**). The area under the curve (AUC) represents the model's average precision, which for the classifier, was 0.93 (95% CI: 0.925, 0.935; $p = 4.54 \times 10^{-2}$).

Another metric used to evaluate the classification model was the F1 score, which was derived from the precision and recall values. This score is frequently used in the evaluation of classifiers.[11] The highest F1 score achievable across all thresholds on the precision-recall curve was 0.875 (95% CI 0.817, 0.933; $p < 0.001$). At this score, the precision was 82.4% and the recall was 93.3%.

Segmentation

The ability of the area of the predictions to estimate haemorrhage size was analysed. The mean value of all the pixels in each original mask in the testing dataset was calculated, along with the mean value of all the pixels in each predicted mask. This was used as a marker of mask area. The predicted mask was given a threshold to make the output binary, as described above. The correlation between the pairs of mean values for each image was calculated over a range of classification thresholds, and the threshold with the highest Pearson correlation coefficient was chosen. This threshold was optimal for the validation data (note that further evaluation on clinical data would be needed to optimise this for different applications). As previously described, the model was evaluated on the validation dataset (n = 127), which was set aside from the training data. The correlation coefficient at this threshold was 0.80 ($p < 6.5 \times 10^{-29}$).

Having determined the optimal threshold for optimum prediction, the accuracy of segmentation via this model at this threshold was analysed. The Intersection over Union (IoU) metric was used to evaluate the model's segmentation performance; this quantifies the overlap between the radiologist's segmentation of an image and the model-based segmentation.[12] Across the pathological cases in the testing data, 71.6% (95% CI: 67.5%, 75.7%) of the segmentation of images matched the radiologist's original segmentation; this was true even when the model falsely predicted haemorrhage in a normal scan.

A collection of randomly selected predictions from the model at the optimal threshold, alongside the associated scan and radiologist segmentation is presented in **Figure 5**.

Discussion

With regards to use of the model as a classifier of disease (haemorrhage), the precision-recall AUC value observed in this study (0.93) was in line with a similar study, by Monteiro *et al.*, which obtained an AUC value of 0.89 (CI 95%: 0.86, 0.91).[13] Notably, the model used in the previous trial was evaluated on an external validation set, increasing its reliability.[13] Monteiro and colleagues also used receiver-operator characteristic (ROC) curves in their analysis, which have been shown to be comparable to precision-recall curves.[14] However, precision-recall curves are better for analysing rare findings due to their ability to focus on uncommon pathological results versus frequent normal results.[15]

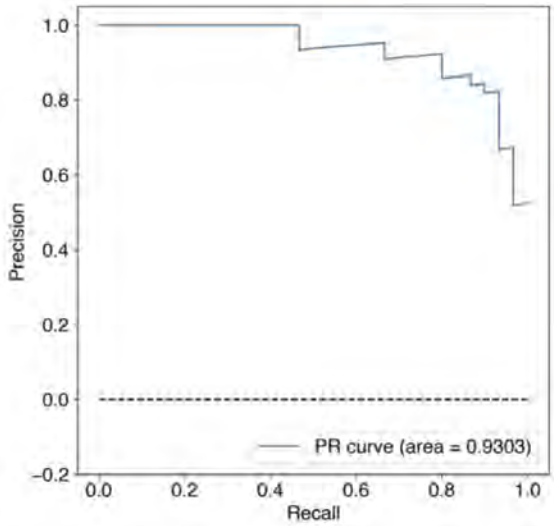

Figure 4. Precision-recall curve for haemorrhage classifi ation. The precision-recall curve for the model as a scan-wise classification algorithm. PR, precision-recall.

In the present study, the model thresholds for both the F1 score and correlation coefficient were set at the maximum that could be achieved for the validation dataset. In order to assess the model's maximum thresholds in a clinical setting, a clinical dataset would be required for use in the model evaluation, using the same analysis as in this study to optimise the thresholds. This would set the balance between recall and precision needed for a given application. This technique is commonly used for this class of problems but it is difficult to optimise the model without large amounts of validation data.[16]

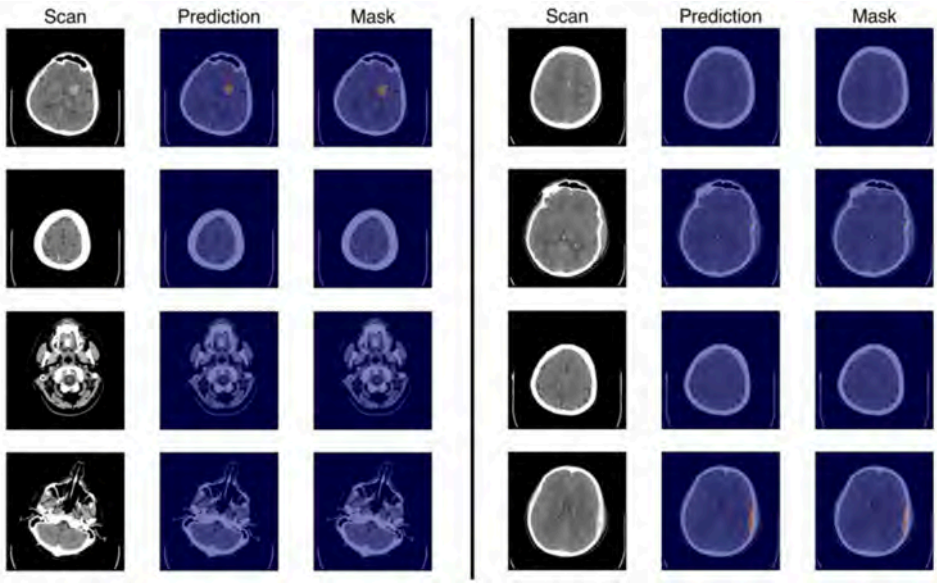

Figure 5. A collection of test scans, showing predictions from the final model, and radiologist segmentations. More predictions can be found in the GitHub repository: https://github.com/freddie-renyard/CT-Segmentation-UNet. Scan images from Hssayeni (2019).[6]

The maximum F1 score was 0.875; this value was derived from the same metrics as the precision-recall AUC but gives a less abstract indication of model performance. A precision of 82.4% at a recall value of 93.3% would restrict the model's use to highlighting areas of potential haemorrhage to a radiologist, rather than autonomous diagnosis. Validation with clinical data against radiological diagnosis would confirm or refute this claim. Another study, which focussed on classification of cranial CT scans, achieved lower precision and recall scores (67.8% and 61.0%, respectively), but the number of labels being classified was higher, at 9 categories rather than the 2 described here.[17]

The analysis of the model's ability to predict haemorrhage volume demonstrated the model to be moderately successful, with a significant, high positive correlation of 0.80.[18] However, this performance is inferior to more advanced algorithms; other models have achieved stronger correlations with testing data, with difference in haemorrhage volume estimations ranging from 0.07 ml to 2.09 ml for different haemorrhage classes.[13]

Upon use of the model in this study, segmentation performance on large haemorrhages (IoU = 72%) was lower compared with other medical algorithms; for example, when similar approaches were used to segment cervical muscles on ultrasound, IoU values of over 86% were obtained.[19] The UNet architecture has also been applied to abdominal CT data for segmentation of liver tumours, achieving scores of 92.6%.[20] Unfortunately, the model used in this study has not been tested on small haemorrhage volumes and, so, performance in this respect has not been determined.[13]

The main limitations of this study are:

1. The small dataset. Large datasets are needed for better neural network performance.[4] This has been demonstrated by Montiero *et al*.[13] who conducted a study that used a larger amount of data than this study for voxel-wise segmentation, which involves processing an entire scan with 3D data.
2. The lack of external validation. The only data that the model was analysed on is that of the dataset provided by Hssayeni *et al*.[6] Although the data analysed was withheld whilst training the model, evaluation of clinical data would be needed to determine the optimum threshold for use in the analysis.

Overall, the architecture used was not sufficiently complex to produce results at performance levels comparable to other studies that has used machine learning for analysis of CT data. However, its application to other real-time imaging modalities, like ultrasound, is more suitable as the model is small, potentially enabling predictions from the model (inferences) to be made locally and in real time using the computing resources available at hospitals. This has the benefit of local data processing, rather than sending data to a remote server, which could compromise data security.[21] In light of this, further experiments were performed to adapt the model for use on a portable device application (iPhone) using Apple's machine-learning framework. The model was able to infer segmentations of scans in around a fifth of a second, with potential real-time applications (see **Appendix 1** for details). The CT segmentation algorithm would be less useful in this format since clinicians are trained to pick up major CT abnormalities in emergency settings. However, if this model architecture was trained on ultrasound images and embedded into a portable device, it could assist with interpretation.

Conclusion Machine learning models are often criticised for their black box characteristics, producing diagnoses with no explanation.[22] Segmentation-based models provide an alternative way of analysing scans using machine learning. CT is a good imaging modality for use with an advanced model that can extract large quantities of analytical information from the scan, despite being slow to execute, as the scan is performed once and the data can be saved to be viewed later. Ultrasound would be a better imaging modality for implementation of this model's architecture (U-Net) as the images change in real-time, and this model is small enough to produce rapid, offline inferences (so-called 'AI at the edge').[23] This could provide a heatmap of the image to help identify structures for ultrasound-guided nerve blocks or IV access, helping clinicians to interpret difficult imaging.

In general, convolutional neural networks will perform better when more data is available.[8] Developing better algorithms for machine learning models majorly depends on the availability of large datasets of anonymised patient data. This is important in healthcare, where data is scarce due to confidentiality but where models must be trained to high levels of accuracy to ensure that diagnoses are not missed.

Acknowledgements Many thanks to Ben Lippold (University of Bristol, Bristol, UK) for giving the author access to his graphics card and TensorFlow environment to train the final model.

Contribution statement The author confirms that they were substantially involved in the analysis and interpretation of the data, along with being substantially involved in the model development. The author also drafted the work and revised it.

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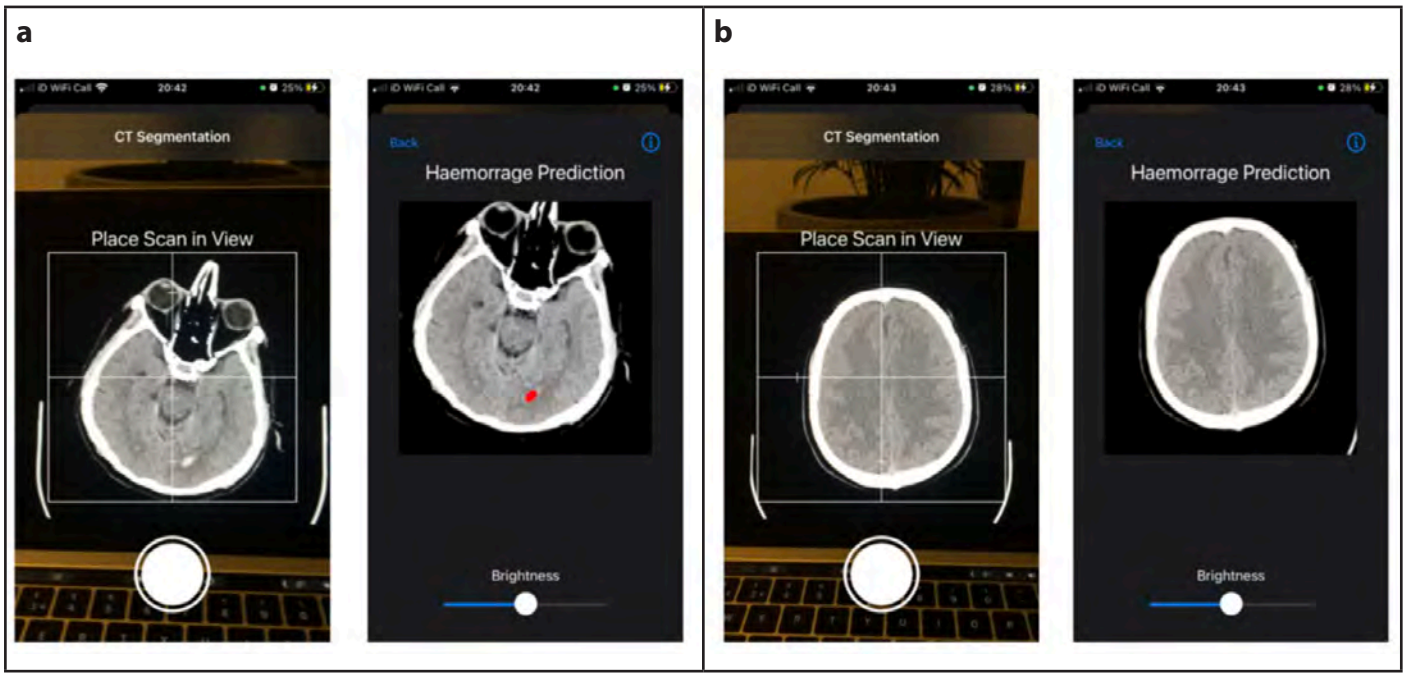
Appendix 1: Adapting the model for use on an iPhone using Apple's machine-learning framework

In order to test the model's speed on a device with a relatively small amount of computational power, a model was created for use on the iPhone using Apple's Core Machine Learning tools. This is a feature that the company is gradually making more powerful, along with adding more hardware to speed up AI applications on the device.[24] Some screenshots of the app's results on normal and haemorrhagic scans from the test data are given in **Supplementary Figure 1**.



Supplementary Figure 1. A collection of screenshots from the test application built on the iPhone. The scans are derived from the test dataset used in the main study (https://www.kaggle.com/vbookshelf/computed-tomography-ct-images). (**a**) A scan that is positive for haemorrhage, as confirmed by a radiologist. (**b**) A normal scan.

The app was tested on the iPhone 6S and, even with this older hardware, the model was able to process a request and display the result in a mean time of 0.218 seconds (standard deviation = 0.017 seconds; n = 5). This indicates that the model could theoretically run at around 4 and a half frames per second on the iPhone 6S, which could be improved with use of newer devices with specific AI hardware. These sorts of applications of AI on the edge could be used for real-time interpretation of imaging mediums, like ultrasound, which could provide an added layer of understanding for images that are often difficult to interpret.

Research Highlights

Chest x-rays as a routine follow up in testicular cancer patients: are they necessary?

Joshua Petersen
Year 5, Medicine, University of Exeter
Email: jp665@exeter.ac.uk

Abstract

The aim of this audit was to investigate if chest x-rays (CXR) are a useful routine follow up tool in patients treated for testicular cancer. It will investigate if guidelines are adhered to and how often the CXR detect metastases. During follow up the patients will receive blood tests for tumour markers, CXR and CT scans. Data for this audit was collected on 94 patients with testicular cancer who had completed their 5 year follow up from 2005 to 2010 in RCHT with 24 patients having to be excluded due to multiple factors. The results of this audit showed that of the 70 patients studied, 8 were found to have metastases with only one of these being found via CXR. All other metastases were discovered on CT scans or via the patient's tumour markers. On average the patients received 8.14 CXR over 5 years with only 62% of patients receiving the required amount during their follow up. There is evidence to show that guidelines could be changed to remove CXR from being part of a routine follow up as CT scans alone are good enough at detecting relapses. Removal of CXR from guidance will reduce the amount of radiation exposure and the possible increase in cancer risk later in life as well as helping to reduce the anxiety involved in extensive follow up treatment and reduce cost. Further research needs to be completed due to a small sample size in only one locality.

Abbreviations

CXR - Chest x-rays

Introduction

Testicular cancer is the most commonly diagnosed cancer in the UK in young men, with around 2200 new cases in 2017.[1] Incidence rates for testicular cancer in the UK are highest between the ages of 30-34.[1] However, survival rates for testicular cancer are very good with 91% surviving for 10 or more years and relapse rate being as low as 5% after 3 years.[1,2] Testicular cancers are classified by the type of cells they begin in, with the most common testicular cancer being a germ cell tumour.[3] Germ cell tumours can be subdivided into seminomas and non-seminomas with the latter group including tumours such as teratomas, carcinomas and yolk sac tumours.[3]

Current UK guidelines recommend that testicular cancer follow up should be for 5 years post radical orchidectomy and adjuvant chemotherapy with physical evaluation, tumour markers, chest x-rays (CXR) and CT scans of the chest and abdomen.[4] Over the 5 years, patients will receive between 6 and 11 CXR depending on the type of tumour and if they have had adjuvant chemotherapy.[4] This is equivalent to 60-110 days background radiation which has the possibility of increasing their risk of developing another cancer.[5] Furthermore patients will receive a CT scan of the chest and abdomen twice in the first year of follow up and once a year after that for 5 years, which is equivalent to another 2 years of background radiation per CT scan.[4,5]

This audit aims to investigate if CXR are a useful routine follow up tool in patients treated for testicular cancer by investigating if the guidelines are adhered to and how often the CXR detect metastases.

Methods

Initial information for this audit was found using PubMed. Searches were refined using certain keywords such as "testicular cancer AND chest x-rays", "seminoma AND chest x-ray" and "non-seminoma AND chest x-rays". Previously written systematic reviews and cohort studies were analysed.

Data was collected on 94 patients (mean age 50.14) with testicular cancer who had completed their 5 year follow up from 2005 to 2010 in RCHT. 24 patients had to be excluded due to multiple factors,

including the patient moving away during treatment, inability to access the patients notes, and the cancer being a relapse or not a primary cancer. The number of CXR patients received during their follow up was recorded, as well as whether any metastases were found and the method used to find them.

Results

Of the 70 patients studied, 50 had a seminoma of differing stages, 13 had a teratoma, 3 had a carcinoma and 4 had a mixed cancer. 8 patients (11%) were found to have metastases at some point during the 5 year follow up. 2 of these patients had teratomas, 2 had mixed tumours, 3 had seminomas and 1 had a carcinoma. Of those 8, only one of these was detected on CXR with the other 7 being detected on CT and via the patient's tumour markers. The single metastasis found on CXR was also detected on CT, therefore none of the metastases were detected on CXR alone (**Figure 1**). The metastasis detected was a single 5mm nodule in the patient's right lung, which was discovered on the first follow up visit and no treatment was given. The total number of CXR done during follow up in all 70 patients was 570 with metastases being detected on only 1. On average, patients received 8.14 CXR over 5 years (mode=5). At follow up, 44 out of 70 patients (62%) received the required amount of CXR (which depended on the type of tumour that they had).

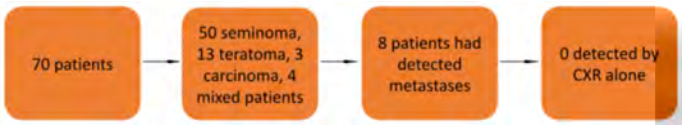


Figure 1. The number of patients, distribution of different tumours, number of patients with metastases, and metastases detected by CXR alone.

Discussion

These results provide evidence to show that CXR could be removed from being part of routine follow up. Testicular cancers have a very low relapse rate, with most relapses occurring in the first 2 years and the chance of a relapse after 3 years being as low as 3%.[3] Therefore, it could be argued that there is no need for patients to receive CXR on follow up.

According to UK guidance, one of the aims of follow up is "to detect relapse as early as possible in each stage".[4] When looking at the results it could be argued that CXR are unnecessary as CT scans detected 100% of relapses. This is limited by the small number of relapses and would be of interest to repeat the study on a larger scale. A study by Kollmannsberger *et al*. which looked at patterns of relapse in patients with stage 1 testicular cancer, found that CT and tumour markers were the best investigations to detect metastases and relapses.[6] In a study of 2483 stage 1 patients, they found that CT detected 63% of relapses, tumour markers detected 28% of relapses and CXR and physical examination detected 0.5% of relapses each.[6] From these results, we can see that almost all of the relapses can be detected by CT scan and via tumour markers alone. However, this study is limited by its single centre nature and the study only following stage 1 patients.

Further studies have investigated how often CXR detect relapses in patients being followed up.[7–11] De La Pena *et al*. investigated 1447 patients with stage 1 germ cell tumours in the Thames Valley and Mount Vernon Cancer Centre between 2003 and 2015.[7] Among the 1447 patients, they found 159 relapses with all relapses detected via follow up CT scans or rising tumour markers. None of the 159 relapses were detected by CXR. Gietama *et al*. investigated 290 patients with disseminated non-seminomatous testicular cancer between 1977 and 1999.[8] They found that 33 of the 290 patients relapsed; CXR was not involved in the detection of any of these relapses. Gels *et al*. investigated 154 patients with stage 1 seminomas between 1982 and 1992.[9] They found that 42 of the 154 patients relapsed with none of these relapses being detected on CXR. Rathmell *et al*. followed 29 relapse patients whose cancer recurred following treatment for germ cell tumours.[10] Tumour markers were found to be the first indicator of relapse in 55% of patients. They found that CXR discovered the first relapse in 2 (7%) patients. However, several of the patients that they followed had residual masses not removed post chemotherapy which may have influenced the value of CXR in their detection. Tolan *et al*. investigated 527 patients and found that of the 73 that relapsed, none of the relapses were detected on CXR alone.[11] From these studies we can suggest that CXR are not a good tool for detecting relapses in testicular cancer, and that CT scans alone would be enough to detect any possible metastases in patients with testicular cancer relapses, as long as they have had removal of all residual masses.[7–11] The studies also looked at different types of tumours at differing stages of disease and found that the results were the same.

Removal of CXR from routine follow up may help to reduce the anxiety of extensive follow up testing 5 years post treatment, as well as reducing the patient's X-ray exposure. Furthermore, eliminating CXR should result in a financial saving, as well as reducing the waiting times for CXR.

This audit found that only 62% of patients received the correct number of CXR for their type of tumour during the 5 year follow up period. This could be another sign that CXR are not considered to be vital in a patient's follow up. Furthermore, this shows that the guidelines are not being adhered to and this could potentially be a setback of this audit. If all the patients received the correct number of CXR then the results could have been different. Some patients received as little as 2 CXR during follow up, which thus had no effect on detecting any relapses. In particular, one patient with a malignant teratoma received 2 CXR during follow up and was found to have a mediastinal mass on CT which was not detected on CXR. This suggests that CT alone is enough to detect metastases and CXR are not a useful tool at follow up.

Conclusion There is evidence to show that the guidelines could be changed to remove CXR from being a part of the routine follow up of patients treated for testicular cancer. Due to a very low relapse rate for testicular cancers, especially in stage 1 seminomas with adjuvant treatment, it could be argued that there is no need to conduct CXR on patients during follow up. Furthermore, CXR detected a lung metastasis in only one patient, for whom no treatment was offered. As the patients in this study were already receiving at least 6 CT scans, with 4 being scheduled in the first 2 years, this may be sufficient to detect any possible metastases. Therefore, there may not be a need for the patient to also undergo CXR and, consequently, be exposed to more radiation than they need to be, which is associated with a possible increase in cancer risk later in life. Also, removal of CXR from follow up procedures may be helpful in reducing the anxiety associated with extensive follow up treatment and the costs for NHS trusts. Due to the small sample size of this audit, further research needs to be carried out to improve the validity of the results.

Contribution statement The author made substantial contributions to the conception or design of the work, drafted the work and gave final approval of the version to be included in Inspire.

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Research Highlights

Evaluating how the use of patient information leaflets tailo ed to a given condition improve health outcomes

Abyrami Sivanandarajah
Year 4, Medicine, Plymouth University
Email: abyrami.sivanandarajah@students.plymouth.ac.uk

Abstract

Patient information leaflets (PILs) have been widely used over time as a way to give patients governance over their own health. As information becomes more accessible, there is an increased risk of unreliable information being available to the public. This, combined with the limited consultation time in the clinical setting, can cause misguidance and misunderstanding amongst patients. PILs rectify this by providing credibly sourced information to be used outside of the clinical setting. This good-quality information educates and enables patients to make autonomous decisions with the guidance of their physician. However, PILs have been shown to be counterproductive by burdening patients with too much information, as well as altering outcomes in low literacy patient groups. Thus, physicians should evaluate the use of PILs depending on a patient's individual circumstance so as to ensure their effectiveness in improving health outcomes.

Abbreviations

PIL - Patient information leaflet

Introduction

In recent years, there has been a push to move away from a system overseen by paternalism and towards endorsing shared decision-making. Under the guidance of clinicians, patients are becoming more involved in their own medical care, being provided with imperative information that aids their understanding of a given condition.[1,2] The GMC's guidance on consent highlights the importance of working in partnership with patients.[3] The delivery of this information should be fully comprehensible and appropriate to that of the patient's needs or wants, whether that be by advocacy services, patient information leaflets (PILs), patient programmes or support groups.[2,3]

> *PILs are an integral tool that assist patients in making these informed decisions,[4] passing on more power and control to the patient.*

This makes patient engagement crucial for exercising autonomy.[5] However, questions are being raised as to whether PILs improve health outcomes in patients, such as, do PILs lead to neglect of marginalised subgroups of individuals, like those who are illiterate? This article will, therefore, evaluate the advantages and disadvantages of using PILs in clinical practice.

The benefits of PIL

Clearly constructed PILs used as an adjunct to consultations have shown to improve the understanding of a condition by patients,[6] and this can satisfy a patient's desire to be better informed about their health. Following on from this, a meta-analysis found that PILs contribute to better health outcomes in well informed patients.[7] For example, multiple studies observed positive effects on increased knowledge and satisfaction of patients. Using this transparent sharing of patient information has been shown to diminish patient anxiety.[6,7] A study by Kenny *et al* observed how successful information leaflets were in educating patients on prescription medications.[6] It was found that the group of patients who received leaflets on their prescription medication were more satisfied than those who did

not. Regardless, 97% of patients thought PILs accompanied with prescription medication were a good idea. In addition, the use of PILs in the treatment of patients with rheumatoid arthritis demonstrated reduced rates of depression and pain, suggesting improvement in both physical and mental health domains. This provides a reason to link PILs to better health outcomes.

Sustersic *et al* conducted a study to analyse the impact of PILs on doctor–patient communication in the context of acute conditions presented to two emergency departments in France. It was discovered that PILs improved doctor–patient communication, patient satisfaction scores relating to healthcare professionals, and promoted good medical practice amongst doctors.[4] In the PIL intervention group, more physicians carried out investigations in practice, such as examinations and laboratory analyses, and there was a reduced number of drug prescriptions. It is arguable that this may be the result of PILs improving the dialogue structure between patients and doctors, and PILs acting as a firm reminder for physicians to monitor their drug prescribing.

> *Thus, PILs can augment patient outcomes through educating both patients and doctors on better medical practice.*

PILs used in consultation have also been shown to improve adherence to advice and medication.[7] With the implementation of PILs, it was found that there were fewer consecutive visits from patients after initial consultation. For example, Sustersic *et al's* study of patients with lower back pain showed that information leaflets supported these patients by improving their confidence and adherence to guidance.[7] Consequently, more of the patients were found to apply the information provided within the leaflet, including the recommended exercises, to aid their lower back pain.

As early as 1972, physicians have faced the on-going issue of patients forgetting or misinterpreting the information discussed during a consultation.[6] It is common for patients to feel overwhelmed by the vast amount of information given to them by clinicians and this creates a stressful environment. Unsurprisingly, this can lead to patients struggling to retain the information given outside of the clinical setting.[2,6] Studies have shown an increase, from 20% to 50%, in patients' abilities to recall the information given to them by physicians when a written or visual input is introduced.[6] Even though verbal advice may be deemed adequate, additional forms of educational material, such as leaflets, stand as the most commonly used way of relaying health information.[6] The written information acts to reinforce the discussion during consultation.

As information becomes more accessible via the internet, patient information can be wrongly construed. PILs can be introduced to hamper the number of patients relying on these inaccurate online sources of information. The content of PILs is constructed using evidence-based knowledge. Thus, patients who use PILs are more likely to have a core understanding of information from these trusted sources.[8] In educating the patient, patients can be given a core framework of knowledge, enabling them to judge the reliability/quality of resources found online and make their own informed choices when it comes to applying medical information.

Time restraints on consultations place increasing onus on clinicians to provide information outside of the clinical setting.[5] PILs seem most appropriate to hand to patients when consultations are restricted to a mere ten minutes. Having a PIL breaks up the amount of verbal communication required and reinforces the discussion during consultation. Patients are also able to take away the PIL, refresh their understanding of what was discussed with their physician and review their knowledge of the condition. Sustersic *et al* (2019) explain that within the quick-paced environment of emergency departments, there is little time for doctors to clearly provide information to patients.[4] Thus, PILs are valued in this context, as the information given during consultation is more likely to be respected and retained, even after the patient has returned home.

> *Furthermore, patients may be prompted to question their healthcare more when a PIL is introduced.*

Moreover, an emergency department environment, such as that used in Sustersic *et al's* study, can be stressful for a patient. PILs given in an emergency setting could encourage patients to adhere to their doctors' advice, so that they do not find themselves in this high-pressure environment again; hence, patient adherence to the guidance given in an emergency setting could be higher than that seen in primary care.

The limitations of PILs

Clinicians are able to gauge a patient's level of understanding and determine how to best adapt their use of terminology to explain a given condition.[8] PILs, however, have no such ability to adjust the information given to suit the patient's knowledge. Thus, the application of PILs in educating individuals with low literacy is limited greatly, as these individuals may lack the ability to read simple written information.[5,9]

> *Amounting to 20% of the UK adult population, individuals with low literacy are an important group to consider when creating informative PILs.*

There are a range of patient demographics that make an individual more vulnerable to low health literacy, such as old age, chronic illness or disability, low socioeconomic status, being of ethnic minority and reduced language proficiency.[5] In Herber *et al*'s study, patients with a migration background were described to heavily rely on their practitioners to grasp health information, regardless of whether a PIL was provided.[10] Thus, encouraging patient engagement via PILs is massively hindered in these already disadvantaged patients. To be beneficial to low literacy audiences, PILs should be presented in a format that is clear and in plain English.[9] They also should include information that signposts patients to other sources, such as online websites that could aid in the understanding of the PILs and, therefore, help to reduce the inequalities between patients with low and high health literacy.

Since some patients may not be able to read PILs, PILs alone are not enough to encourage patient education. PILs require some level of patient input; primarily, it is essential for patients to be motivated enough to read and understand the PIL given to them to result in beneficial changes.[6,7] Some patients disregard PILs because they do not wish to know more about their condition. In addition, PILs that focus on general health were found to be more neglected by patients than tailored PILs that were given to a patient for a specific condition.[6] This could imply that PILs are more effective when there is a level of tailoring to suit the patient's individual needs.

As previously mentioned, some studies have indicated improved doctor–patient communication following use of PILs.[4] However, in their 2019 study, Sustersic *et al* observed that patients that were not given PILs demonstrated similar adherence to advice given by physicians as those given PILs.[4] One possible explanation for such a finding could be put down to an overload of information given to patients who received both oral and written forms of communication. However, PILs have been shown to mitigate information overload and, therefore, further studies are required to investigate this area.

Conclusion

The effectiveness of PILs is dependent on how much a patient wishes to know about their diagnosis. In other words, PILs cannot be used uniformly for every patient. When used, however, there is evidence of improved health outcomes. Employment of PILs in consultation should be at the physician's discretion and dependant on whether they believe their use is suitable for the situation and the patient's individual needs or desires.

It may not be appropriate to use PILs to educate minority groups, such as those with special needs or of lower health literacy. Adopting an alternative and more accommodating method of delivery of information may be more beneficial than PILs for these individuals.

PILs also require consistency in terms of quality of information and content. There is evidence for varying information in PILs across different hospital trusts, with some containing information deemed inadequate when compared to others.[9] The absence of national set standards to rectify these faults perpetuates the improper use of PILs in clinical settings. Consequently, further studies should be conducted to confirm whether PILs, on a national scale, are at a suitable standard.

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Senior Editors, Winter 2021-22

Haleemah Asharaf

Cardiff University

Hello, my name is Haleemah Asharaf and I am a fourth year medical student reading at Cardiff university. I have a keen interest in medical education alongside having a curiosity in the development and integration of technology and artificial intelligence within medicine. The appeal of being a senior editor for this journal stemmed from my desire to be more involved in the research process alongside my passion to evolve my critical appraisals skills, academic writing, and general medical research knowledge. I identify with the journal's goal to immerse students into research through various mediums and hope that our work as a team will encourage our readers to take academic opportunities as a student and as future clinicians. I am elated for the opportunity to aid the progression of many student's research to publication and look forward to contributing to the Inspire journal.

Ellie Best

Cardiff University

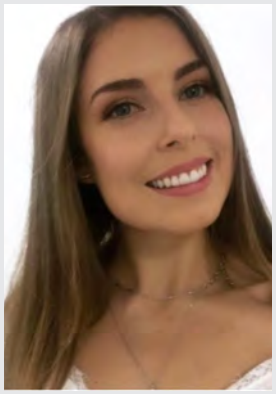
I joined the INSPIRE team last year as I really wanted to learn more about the publication process. Since completing my intercalated degree, I have become really interested in completing more research and becoming an INSPIRE Editor seemed like a great way to experience a different side to the research process. We also launched the INSPIRE Podcast this year, which was designed to increase engagement in research and help communicate novel research in a fun and accessible way. I have had the chance to chat to some incredible students and academics about their research and I have really enjoyed being part of this amazing team. Creating a podcast is something that I had always wanted to do, and this process allowed me to learn more about editing and promoting a new podcast. As an editor, I was able to develop my peer reviewing skills and copy-editing skills, which I feel are really important skills to be aware of when writing or submitting your original research to journals. I have learnt so much over the last year and am really grateful for my INSPIRE experience! The INSPIRE Journal is a great way of getting your undergraduate research published and I thoroughly enjoyed my experience as an editor. I would really encourage anyone who is interested to apply to get involved next year!

Sam Deutsch

Cardiff University

I'm a preliminary year medical student at Cardiff University with a particular interest in neuroscience. I started my medical career at Cardiff in 2020 after graduating from the University of Cambridge with a bachelor's degree in Psychological and Behavioural Science in 2018 and have experience in both Psychology and Medical research. During my undergraduate studies I gained experience presenting at a national BPS conference and focused especially on the neuroscience of addiction and in my interim between undergrad and medical school I worked at the University of Oxford in research into Parkinson's Disease and sleep disorders. I continue to work in the field of neurodegenerative disease research alongside my studies. I am passionate about research and am involved in education with secondary school students in psychology and clinical neuroscience, as I believe being at the forefront of discovery in such a currently pioneering field is something that can really demonstrate the excitement and enjoyment of research to future medics!

Seanain Henry



University of Plymouth

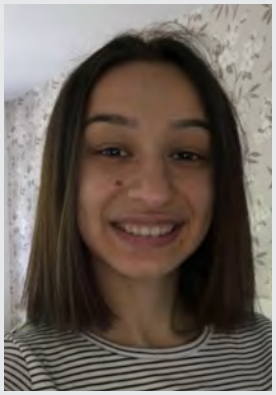
Hi, I'm Seanain and I'm a third year postgraduate dental student at Plymouth University. My journey with INSPIRE started during my undergraduate degree when I undertook a research studentship to develop a chair-side biomarker test for periodontal disease. I have really enjoyed being an editor for the journal this year. Coming from managing a small dental society magazine to working with a fantastic group editing the INSPIRE journal, I have learned so many skills which I know will transfer into my career once I graduate. I particularly enjoyed the creative aspect of the journal. I worked in a small team dedicated to the design and compilation of the journal meaning we could each discuss and add our own touch to both editions. Furthermore, having the chance to work directly with authors to improve and publish their work was very satisfying. It gave me a better insight into the peer-review process from an editor point of view and what makes a good submission. To anyone deliberating whether to get involved in any such way, you won't regret it.

Qui Lim

University of Bristol

I am so grateful to have had this opportunity to be a senior editor and be a part of a fantastic team for the INSPIRE Journal this year. This experience has given me an insight and understanding to the publishing process, and shown me the range of skills, knowledge and people which are required to create the finished piece. As editors, we were also given the freedom to use our creativity and ideas to shape the journal to our envisions; I was particularly involved in the formatting/ style and appearance of the journal, as well as hosting the first training session and creating a support group for our peer reviewers. I also featured on the newly founded INSPIRE podcast which was launched this year, which was a fun opportunity to bust some myths and misconceptions in dentistry. For me, this has been a fantastic thing to be involved with, especially during the pandemic; we met regularly online throughout the year, and it was a great opportunity to work with other students from different universities, learn and develop skills used in the publishing process, including academic writing and critical appraisal skills. I would definitely recommend getting involved with INSPIRE if you're interested.

Anastasia Mirza-Davies

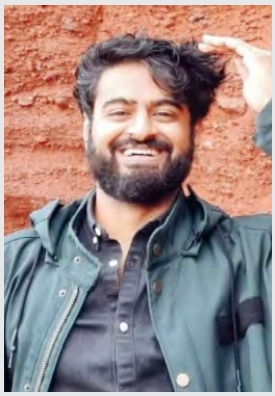


Cardiff University

I'm a final year medical student at Cardiff University and first became interested in research after completing a summer vacation studentship examining the role of the complement system in schizophrenia. Being an editor for INSPIRE has provided a fantastic opportunity to develop key skills in teamwork and leadership. In particular, it has allowed me to meet like-minded editors and peer reviewers from a number of different institutions and disciplines.

Senior Editors, Winter 2021-22

Rajeev Ravi



University of Plymouth

Hello all, I'm Rajeev, and I'm a post-graduate 4th Year Medical Student at Plymouth University. I've really enjoyed being a Senior Editor for the INSPIRE this year as I've been able to learn about various topics across the scientific field submitted by our excellent authors. As an editor this year, I directly contributed to the journal and impacted the issue you are reading now. I worked with a small sub-team, and I was able to explore my creative side and implant my ideas on how the issue could be improved from previous years. Being an author for the journal and now a senior editor, I have found that I have improved my leadership skills, making decisive decisions, time management, and notably my knowledge in and around medicine, which will be helpful in my aspirations of being a surgeon. I am also grateful to have made a wonderful group of friends I wouldn't have met without INSPIRE, and I would highly recommend you get involved, whether through submitting a piece of work or impacting the next issue directly by being an editor. Thank you, I hope you enjoy reading our issue and please reach out to the team if you would like to know more.

Yusuf Sarwar

University of Exeter

Hi, I'm Yusuf - a 3rd year Medical student at the University of Exeter. I am passionate about becoming a research-driven physician and contributing to medical breakthroughs that can provide innovative and novel therapeutic options for patients whilst hoping to influence health policy and potentially impact on a wider scale. This stems from my experience having undertaken a number of fascinating research projects at various institutions. These experiences have given me a deeper appreciation for medical research and the benefits this may have on everyday life. Being a senior editor for the INSPIRE journal has allowed me to also continue building on the necessary skills required for a research-driven career. Being on the INSPIRE editorial team has been a fantastic opportunity which I would highly recommend to anyone deliberating, it has given me an insight into research from perspectives I never would have previously considered!

Natasha Singhal

University of Plymouth

I am a third-year medical student at University of Plymouth. I had previously been involved in many aspects of the INSPIRE programme, which includes conducting a retrospective study as part of the INSPIRE summer project in first year and publishing in an earlier issue. Through these experiences, I realised that clinical research excites me, and I wanted to delve into and explore the opportunities it presents. I identified with the journal's initiative to empower students to explore the fantastic world of research. As a Senior Editor, I hope I have encouraged students and supported them through an academic publication process. This role has helped me refine skills such as academic writing and peer-review skills for clinical research which is an important part of clinical practice. This year, I have also Co-Hosted and Co-Founded the INSPIRE Podcast with three other members of the senior editor team. This successful podcast is designed to discuss the latest research in medicine, dentistry and veterinary medicine with students and academics in a language that everyone can understand. I have enjoyed this experience and learnt many skills and have broadened my interest in reading medical and non-medical literature and explored various perspectives.

Virginija Vilkelyte

University of Exeter

Ever since starting my degree in medicine at the University of Exeter, I had an underlying interest in the research that forms the basis for overall concepts in clincal medicine. Being an INSPIRE student journal editor has indeed allowed me to explore this interest and develop an insight into the field of research, which is otherwise not as often explored in medical schools. Another aspect of my interest in this journal is the values and goals that it upholds. Aiming to be an accessible journal for students across the nation, I believe the INSPIRE journal provides a fantastic opportunity for motivated students making me grateful to be a part of the editorial team. As a current second-year student, I hope to continue my work with INSPIRE for many years to come as I wish to incorporate research in my future and encourage others to do the same.

Unaiza Waheed

University of Exeter

I'm a final year medical student at the University of Exeter with a keen interest in Medical Education and Research. I have experience in delivering national conferences to medical students and university applicants alike. I have also presented at international conferences and published in prestigious journals. I strongly identify with the need to encourage students to partake in research projects, understand the publication process, and effectively disseminate their findings, which is where my role as senior editor for the INSPIRE journal is relevant. I have an intercalated degree in Neuroscience, and my current area of interest is the role of Motor Simulation Theory in the Rehabilitation of Stroke Patients. Next year, I will be undertaking the Academic Foundation Programme and completing my Postgraduate Certificate in Clinical Education alongside my training. My interests outside medicine include reading, photography, yoga and pilates, and brunch with my pals!

Aimee Wilkinson

University of Bristol

It has been such a pleasure to work as a senior editor of the Inspire Student Journal this year. In particular, I have loved working with such a talented team of editors and peer-reviewers to create this journal edition. A key highlight of the year for me was hosting the first ever peer-reviewer training session, which brought reviewers together to learn more about the importance of peer review and how to critically appraise scientific literature. From my experience as a senior editor, I will take away a greater appreciation for the role of teamwork that is embedded in the publishing process. My newfound understanding of what makes a good paper will also undoubtedly assist me in my future career. I am so grateful for the opportunity to take on this role and would recommend becoming involved in the Inspire Student Journal to anyone.

Advisory board, Winter 2021-22

Aarti Jalan,
University of Bristol

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Weronika Nasterska,
University of Plymouth

King-David Nweze,
University of Plymouth

Temidayo Osunronbi,
University of Plymouth

Christina Wainer,
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Cardiff University

List of referees, Winter 2021-22

Lispeth Abraham, *University of Exeter*

Fatima Adamu-Biu, *Oxford University Hospitals NHS Foundation Trust*

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Ajijola Oyedele, *Cardiff University*

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Tushar Rakhecha, *University of Bristol*

Charlotte Reid, *University of Exeter*

Anna Richards, *University of Exeter*

Paul Rival, *Southend University Hospital*

Muskaan Sharma, *University of Plymouth*

Jacob Tan, *University of St Andrews*

Isobel Taylor, *University of Bristol*

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Benedit Turner, *Imperial College London*

Lara Wirt, *Cardiff University*

Idrees Zafar, *University of Plymouth*

The INSPIRE scheme is coordinated by the Academy of Medical Sciences and supported by the Wellcome Trust

University of Bristol

www.bristol.ac.uk/medical-school/study/undergraduate/inspire
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Leads: Elizabeth Coulthard, Associate Professor in Dementia Neurology;
Richard Coward, Professor of Renal Medicine and Consultant Paediatric Nephrologist;
Linda Wooldridge, Chair in Translational Immunology

University of Cardiff

http://cures.cardiff.ac.uk/inspire

Lead: Colin Dayan, Professor of Clinical Diabetes and Metabolism

University of Exeter

https://medicine.exeter.ac.uk/study/ug/medicine/researchopportunities

Lead: Joanna Tarr, Senior Lecturer, College of Medicine and Health

Plymouth University Peninsula School of Medicine and Dentistry

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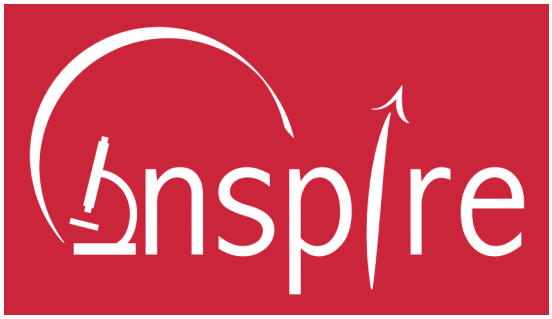
Leads: David Parkinson, Professor of Neuroscience;
Vehid Salih, Associate Professor in Oral & Dental Health Research



Student Health Sciences Research Journal

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