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Welcome to the Autumn 2021 issue of the *INSPIRE Journal*: created by students for students

Hello and welcome to the Autumn 2021 edition of the INSPIRE Student Health Sciences Research Journal. In a collaborative effort between the universities of Bristol, Cardiff, Exeter and Plymouth, the INSPIRE Journal was created as part of the INSPIRE scheme to provide a platform for medical, dentistry and veterinary students to get involved in the publication process. In doing so, the journal supports the INSPIRE scheme's aims to provide students in medical schools across the UK with an opportunity to experience research and to encourage them to incorporate research into their chosen career path. This issue is written and peer-reviewed by students and the whole editorial board is composed of students, making this a true student journal.

2021 has been a strange year and as we enter into a new phase of the pandemic, with a greater sense of freedom, we embrace a hopeful change within healthcare. Both students and professionals have had a difficult year and a half, managing new regulations surrounding PPE, aerosols and maintaining social distancing while trying to deliver the best care for our patients. It certainly hasn't been easy. Additionally, online teaching has taken the forefront in many ways and students have had to rapidly adapt to this version of blended learning.

Despite the lack of face-to-face laboratory time, the evidence base continues to grow, and this edition of the journal demonstrates just that. Bringing together reviews, opinion pieces and articles related to medicine, dentistry and veterinary science, it encompasses your passion for research and advancements within a range of professional fields.

Working primarily with print in the past, we too are moving with the times and present a growing online platform. This year has seen the creation of the INSPIRE Research podcast, inviting a range of known speakers to debate key issues within our healthcare systems. Furthermore, we've brought our blogs section back to life (see https://inspirestudentjournal.co.uk/resources/), meaning more of you can see your name in print and have greater accessibility to an array of research at the click of a button. Make sure you don't miss what we've been working on by following the links below.

On a final note, thank you to everyone who contributed to the journal! We've had a plethora of submissions this year, meaning that we are pleased to be delivering two issues of the journal. To our readers, we hope you find this edition thought-provoking, insightful and inspiring, but most of all we hope it motivates you to get involved in the publication process in whatever way suits; whether it's as an author, peer reviewer or editor!

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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Is this the real life? Is this just fantasy?: the future of managing dental anxiety with virtual reality

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Abstract

This paper aims to give a brief overview of the background of dental anxiety including its origins and prevalence, and why the effective management is pivotal to providing quality dental care. The Modified Dental Anxiety Scale (MDAS) is then explored for both its benefit in population wide studies, but additionally its use as a quantifier in daily dental practice when attempting to 'measure' a patient's perceived state anxiety levels. The article finally contemplates current, commonplace methods of managing the anxious patient and attempts to investigate the rising idea of virtual reality technology as an original tool to tackle anxiety in future generations of dentistry.

Abbreviations

GDP – General Dental Practitioner
IV – Intravenous
MDAS – Modified Dental Anxiety Scale
VR – Virtual reality

Fear *(noun)*
"The emotion of pain or uneasiness caused by the sense of impending danger, or by the prospect of some possible evil."
Anxiety *(noun)*
"Worry over the future or about something with an uncertain outcome; uneasy concern about a person, situation, etc.; a troubled state of mind arising from such worry or concern."
Phobia *(noun)*
"A fear, horror, strong dislike, or aversion; esp. an extreme or irrational fear or dread aroused by a particular object or circumstance."
- Oxford English Dictionary, 2021

Conventionally managing dental anxiety

Dental phobias and anxiety surrounding anticipated dental pain are confounding factors regarded as principal barriers to good dental care, often resulting in appointment avoidance. With the acquisition of >66% of phobias originating in childhood, the predicament can be deep-rooted and difficult to manage.[1]

> *Dental anxiety frequently stems from the patient's anticipated perception of noxious stimuli, or pain, prior to commencement of procedures, often from past negative experiences.*[2]

For the clinician to contend with this, whilst providing optimum patient-centred care, anxiolytic relief is quintessential from the offset.[3]

Dental professionals possess a plethora of methods readily implemented in practice to quell anxiety. These approaches can be pharmacological, such as conscious sedation, or non-pharmacological, such as patient behaviour management (see **Table 1**).[4] The latter is always introductory due to its inexpensive and non-invasive nature; however, it can be ineffective for severe phobias or for longer procedures, such as extractions, resulting in the need for pharmacological intervention.

Table 1. A non-exhaustive list of pharmacological and non-pharmacological management options for the dentist to consider.

Pharmacological	Non-pharmacological
Oral Premedication *Low dose benzodiazepines may be prescribed to anxious patients prior to treatment, for example, to aid in getting a good night's sleep beforehand, or to make travelling to the practice (under supervision by a chaperone) more bearable.*	**Desensitisation** *This is where the patient is gradually exposed to the stimuli that triggers anxiety. For example, in a dental scenario, an initial desensitisation visit may be as simple as asking the patient to sit in the dental chair for a verbal consultation. This way they can become accustomed to the surroundings and the dental team, and slowly gain the confidence to undergo more invasive treatments as appointments progress.*
Inhalation sedation *Titrated nitrous oxide and oxygen are inhaled by the patient nasally via a mask. This can be used as a standalone or as an adjunct to intravenous (IV) sedation during cannulation.*	**Tell, Show, Do** *A commonly used technique in paediatric dentistry, which is also valuable when treating anxious patients. 'Tell' is where the dentist explains the procedure step by step. 'Show' is where the patient is introduced to the equipment to be used such as how it sounds, feels, looks, etc. (Note: This step should be avoided if the instrument is likely to trigger more fear e.g., needles before injections). Finally, 'Do', the dentist carries out the procedure as closely as just explained to the patient, this way they feel informed and more in control of the situation.*
Oral sedation *Oral or transmucosal midazolam is administered to the patient. This is a useful technique when inhalation or intravenous methods are contraindicated, for example, if the patient is extremely needle-phobic, however it is a less predictable method.*	**Distraction** *This is anything that prevents the patient from concentrating on the stimulus causing fear. For example, encouraging the patient to talk about their hobbies to distract from the dental surrounding.*
Intravenous sedation *Midazolam is given intravenously, usually through a cannula in the back of the hand, using a titrated dose dependant on the patient's response. It has a very fast onset of around two minutes but can take up to an hour for the final increment to wear off after treatment.*	**Hypnosis** *This can be defined as an altered state of consciousness where the patient is more susceptible to suggestion. One visualisation technique used is the 'Comfort Dial',[5] the patient is asked to visualise a dial from zero to ten, zero being most comfortable and ten indicating pain. The patient visualises a dial of their own choosing and over several rehearsal sessions learns to respond to the suggestion of lowering the pain they feel by turning down their dial.*
General anaesthetic *This is where the patient is 'put to sleep' so they are completely unaware of their surroundings and the procedure taking place. Avoided, where possible, due to associated risks.*	

Measuring dental anxiety

A valuable screening tool used to determine levels of patient anxiety is the Modified Dental Anxiety Scale (MDAS).[6] Its intended use is in population-based studies, however, MDAS is also a screening tool for the General Dental Practitioner (GDP) on a case-by-case basis if a patient's need for sedation is to be assessed. It is divided into 5 segments, each scored 1-5, with a maximum achievable score of 25. Any score greater than 19 denotes severe anxiety or phobia and can primarily indicate the necessity for pharmacological intervention.

It is preferable to avoid the use of pharmacological agents, where possible, due to the risks associated with each drug and procedure. Therefore, several novel techniques have arisen to circumvent this matter.

Novel methods of management

In the last decade, virtual reality (VR), a technology that allows for combined fully-immersive audio-visual sensory stimulation, has made an emergence and its practical uses as a distraction technique are now being explored.

Attention-demanding distraction tasks are known to reduce anxiety-related distress exhibited in response to noxious stimuli. Increasing the attentional capacity demanded from said tasks further reduces the distress exhibited. This is thought to be partly due to the psychological nature of the perception of noxious stimuli. Hence, if a patient's focus is elsewhere when experiencing a situation that would ordinarily trigger anxiety, the anxious feelings are perceived less intently than with no distraction in place.[7,8]

> *Engaging with VR requires a large portion of the attention span due to its immersive nature and, therefore, results in less perception of anxious feelings during dental treatment.*

VR is non-invasive, non-addictive and its frequency of use does not correlate with diminished efficacy; therefore, it demonstrates strong potential as a feasible tool to manage anxiety in a variety of healthcare settings.[9] Despite this noticeable potential, dentistry, as a field, has received little attention from VR researchers and studies of VR in a dental context are scarce.[10]

Ougradar *et al* are among initial proprietors for the research into the use of VR distraction to manage dental-based anxiety. Fifty patients were pre-screened using MDAS to determine anxiety levels prior to extractions. All patients included had previous history of having experienced a dental extraction. The procedure was carried out using a Virtoba VR headset simulating the patient being under the sea. Following the study, responses showed that 87.5% wanted VR to be used during their next appointment, suggesting VR relieved some level of dental anxiety or at least made the experience more bearable than having an extraction without the use of VR.[11]

Summary and conclusions

VR holds promising potential as a tool to aid treatment of the anxious patient, but there are drawbacks. Some patients have reported motion sickness associated with the use of VR, meaning it may not be tolerated by all users.[12] Cost of the equipment and availability, as well as sterilisation of the units, are also areas to be considered if VR is to become commonplace within the dental setting.

Additional research with larger sample sizes and varied patient groups are necessary to explore these ideas further. Despite this, rapid technological advances hold potential for the future of fear-

free dentistry and, hopefully, this avenue of thought will receive increasing attention from researchers during this generation of dentistry and the next.

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References

1. Milgrom, P., Fiset, L., Melnick, S., et al. (1988). The prevalence and practice management consequences of dental fear in a major US city. The Journal of the American Dental Association, 116(6), pp.641-647.
2. Arntz, A., van Eck, M., Heijmans, M., et al. (1990). Predictions of dental pain: The fear of any expected evil, is worse than the evil itself. Behaviour Research and Therapy, 28(1), pp.29-41.
3. Ram, D., Shapira, J., Holan, G., et al. (2010). Audiovisual video eyeglass distraction during dental treatment in children. Quintessence International, 41(8), pp.673-679.
4. Appukuttan, D. (2016). Strategies to manage patients with dental anxiety and dental phobia: literature review. Clinical, Cosmetic and Investigational Dentistry, p.35.
5. Brann, L., Owens, J. and Williamson, A., 2012. The handbook of contemporary clinical hypnosis. Wiley-Blackwell, pp.326-330.
6. Humphris, G., Morrison, T., Lindsay, S., et al. (1995). The Modified Dental Anxiety Scale: validation and United Kingdom norms. Community Dental Health, 12(3), pp.143-150.
7. McCaul, K. and Haugtvedt, C. (1982). Attention, distraction, and cold-pressor pain. Journal of Personality and Social Psychology, 43(1), pp.154-162.
8. McCaul, K. and Malott, J. (1984). Distraction and coping with pain. Psychological Bulletin, 95(3), pp.516-533.
9. Morris, L., Louw, Q. and Crous, L. (2010). Feasibility and potential effect of a low-cost virtual reality system on reducing pain and anxiety in adult burn injury patients during physiotherapy in a developing country. Burns, 36(5), pp.659-664.
10. Tanja-Dijkstra, K., Pahl, S., White, M., et al. (2014). Improving Dental Experiences by Using Virtual Reality Distraction: A Simulation Study. PLoS ONE, 9(3), p.e91276.
11. Ougradar, A. and Ahmed, B. (2019). Patients' perceptions of the benefits of virtual reality during dental extractions. British Dental Journal, 227(9), pp.813-816.
12. Chang, E., Kim, H. and Yoo, B. (2020). Virtual Reality Sickness: A Review of Causes and Measurements. International Journal of Human–Computer Interaction, 36(17), pp.1658-1682.

How can folic acid prevent anencephaly? The examination of the mechanism behind folic acid and the homocysteine remethylation cycle

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Abstract

Anencephaly is a congenital neural tube defect (NTD) where part of the skull and brain does not develop. Folic acid can reduce NTD development. An NTD occurs when the neural tube fails to close properly during embryogenesis. Women are recommended to take a 0.4mg folic acid supplement daily prior to conception and during the first trimester of pregnancy. Folic acid is a synthetic derivative of vitamin B9. It is important in several mechanisms in the body, including homocysteine remethylation, which is involved in DNA synthesis and repair. Whilst folic acid does play a role in NTD, its effectiveness is likely determined by its correct usage and dependent on other factors. Further research into the effects of too much folic acid is necessary to ensure its safety and continued benefit.

Abbreviations

DHFR - Dihydrofolate reductase
MS - Methionine synthase
5-MTHF - 5-Methyltetrahydrofolate
MTHFR - Methylenetetrahydrofolate reductase
NTD - Neural tube defect
RCOG - Royal College of Obstetricians and Gynaecologists
RCT - Randomised controlled trial
SAH - S-adenosyl-homocysteine
SAHH - S-adenosyl-homocysteine hydrolase
SAMe - S-adenosyl-methionine
THF - Tetrahydrofolate

Anencephaly and prevention

Anencephaly is a neural tube defect (NTD) caused by disturbances of neurulation in early embryogenesis. It results from the failure of neural tube closure between the 23rd and 26th day post-conception.[1] Each case presents with the absence of the calvarium alongside the cerebral cortex, a major component of the human brain composed of tightly packed neural tissue that is responsible for higher brain functions including memory and emotion. Sometimes other elements of the brain are absent, such as the cerebellum **(Figure 1)**. It affects around 1 in 1,000 pregnancies, although most cases lead to miscarriage.[2] It is estimated that 1 in 10,000 infants are born with anencephaly,[3] and the few neonates that survive full-term gestation only live for hours or, at most, a few days. No surgical intervention is currently feasible.[4] Therefore, with such high miscarriage rates and neonatal mortality, it is essential that anencephaly is prevented. To help achieve this, many countries including the UK, Canada and America now advise women planning a pregnancy take a daily dose of 0.4mg of folic acid supplementation before conception and during the first trimester of pregnancy. Folic acid is a synthetic derivative of vitamin B9, whereas folate is the natural water-soluble form of the vitamin.

Figure 1. Hand drawn illustration by author of infant with anencephaly. Noticeable features include absence of calvarium and cerebral hemispheres. Illustration was aided with use of image from Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities.[5]

In this article, the effectiveness of folic acid in preventing anencephaly is considered, whilst research and guidance are examined. Rationale for selection of research material took into account the quality and risk of bias, aided by the Hierarchy of Evidence, which viewed randomised controlled trials (RCTs) and systematic reviews more highly than cohort and case-control studies. Papers were screened using key search terms "Anencephaly", "Folic Acid", "Neural Tube Defect", "Methylation" and "Pregnancy".

Folic acid breakdown and the homocysteine remethylation cycle

The British Dietetic Association states that folic acid is important for the formation of red blood cells, nerve stimulation, DNA and RNA formation and repair.[6] After ingestion, supplemental folic acid is metabolised in the liver by methylenetetrahydrofolate reductase (MTHFR) to 5-methyltetrahydrofolate (5-MTHF).[7] It is then readily absorbed primarily in the small intestine and reduced to tetrahydrofolate (THF) by two reduction reactions that are catalysed by dihydrofolate reductase (DHFR). In contrast, folate, found naturally in fruits and vegetables, is already present in the active form of 5-MTHF.[8] In order to be absorbed in the gut, 5-MTHF must be hydrolysed into monoglutamates.[9] Folic acid and folate become chemically indistinguishable once they have been converted to THF in the enterocytes of the small and large intestine.[10] Therefore, once folic acid is broken down to THF, it is likely to have the same effect as natural folate.

Folic acid plays a role in the formation of the amino acid methionine by homocysteine remethylation **(Figure 2)**. This cycle is important for processes such as nucleotide synthesis. This pathway occurs in several stages: (1) S-adenosyl-homocysteine (SAH) is formed directly from S-adenosyl-methionine (SAMe) through the addition of a methyl group; (2) catalysed by the enzyme SAH hydrolase (SAHH), SAH is further broken down into the amino acid homocysteine;[8] (3) 5-MTHF, the active form of folic acid , as well as methionine synthase (MS), are responsible for converting homocysteine to methionine by the transfer of a methyl group; (4) methionine can then be converted to SAMe, a cofactor for many methylation reactions in the human body, including the methylation of chromatin and proteins;[8,11] (5) the cycle then repeats. Insufficient levels of 5-MTHF can result in a build-up of homocysteine and, therefore, inhibit or reduce the formation of SAMe within the cycle.[8]

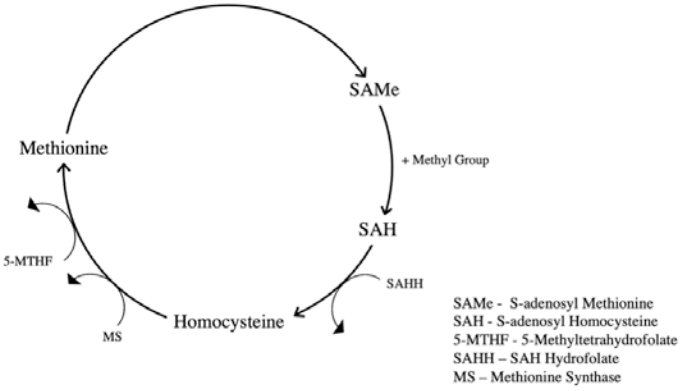

Figure 2. Homocysteine remethylation cycle. Pathway of the homocysteine remethylation cycle, drawn by author. Illustration was aided with use of previous publications.[7,10]

Signifi ance in relation to anencephaly

Importantly, raised plasma concentrations of homocysteine and SAH have been identified in women with pregnancies affected by NTDs.[12] This suggests a possible link between anencephaly and metabolic disruption. Adequate concentrations of folic acid broken down to 5-MTHF may, therefore, be necessary to reduce interference within the homocysteine remethylation cycle and the prevention of homocysteine build-up within the body. An enzyme abnormality within the metabolic pathway could also be a factor in determining anencephaly development. This could include enzymes such as SAHH or MS.[13] Enzyme malfunction could also lead to pathway inhibition and, therefore, cause build-up of substances, such as homocysteine, which could lead to increased anencephaly risk.

One animal study, in chick embryos, analysed the effects of administered homocysteine in the chicks' development and methylation metabolism. Results showed a delayed closure of the anterior neural pore.[14] The failure of the anterior neuropore to close causes anencephaly.[15]

> *Therefore, a lack of folic acid and the subsequent effects of increased levels of homocysteine could well be linked to increased anencephaly risk.*

On the other hand, women who have had pregnancies resulting in NTDs are most often not deficient in folate.[16] This could further support the fact that anencephaly may develop as a result of an abnormality of one of the enzymes involved in homocysteine remethylation, such as MS, rather than folic acid deficiency.

Discussion and conclusion

There is strong evidence to suggest that folic acid is effective in preventing NTDs.[8,17] However, anencephaly will not necessarily develop if the vitamin is not taken during the recommended timeframe. Furthermore, even when folic acid is administered correctly, anencephaly could still develop. Genetics could also play a role; particular ethnic groups are more likely to develop NTDs.[18] There is also research to support that after having a pregnancy with an NTD, the risk of having another increases.[19] One study identified the presence of unmetabolised folic acid in the bloodstream in those who consumed the daily recommendation of 0.4mg, questioning the effect of having too much folic acid.[20] Additionally, papers have suggested that supplementation of folic acid could stimulate cancer progression.[21,22] However, there is conflicting evidence, with some RCTs reporting that folic acid has no effect on specific cancer biomarkers.[23,24,25] The participants of these studies were not pregnant women, which is a limitation.

A further point of study would be to see whether a diet very rich in folate, as well as folic acid supplementation, would exceed the recommended dosage of the vitamin and therefore cause adverse effects. Despite this, a diet rich in folate should not be discouraged since the health benefits of fruit and vegetables are well-documented. There are also instances where mothers are advised to take higher doses of folic acid to prevent NTDs. This includes pregnancies where there have been previous children with NTDs, or where the mother either smokes, is obese, has diabetes mellitus or poor adherence to folic acid is predicted.[26]

In 2018, the Royal College of Obstetricians and Gynaecologists (RCOG) acknowledged that fortification of folic acid in foods, such as flour, would see a "significant reduction in the incidence of NTDs".[27] This evidence is supported by early RCTs which concluded supplementation with folic acid is an effective preventative measure against most NTDs.[28,29] Despite this, fortification is not implemented in all countries for the following reasons: financial cost; challenge in accessing resources to roll out large-scale projects; fortified foodstuffs, such as flour, may not support a country's classic diet.[30] Also, in countries where there are high unplanned pregnancy rates, women may be unaware of the need for folic acid supplementation at pre-conception, conception and first-trimester periods.[31]

In conclusion, folic acid can be an excellent primary strategy in preventing anencephaly. To move forward, more research into the

consequences of higher folic acid levels and possible cancer risks is required.

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References

1. O'Rahilly M, Muller F. Human Embryology & Teratology. New York: Wiley-Liss; 1992.
2. Cook RJ, et al. Prenatal management of anencephaly. International Journal of Gynecology and Obstetrics. 2008;102304–308.
3. Anon. Genetics Home Reference. Anencephaly. Available from: www.ghr.nlm.nih.gov/condition/anencephaly#statistics. Accessed: 17 November 2019.
4. Fetal Health Foundation. Anencephaly. Available from: www.fetalhealthfoundation.org/fetal-syndromes/anencephaly/. Accessed 17 April 2021.
5. Centers for Disease Control and Prevention. Facts about Anencephaly. Available from: www.cdc.gov/ncbddd/birthdefects/anencephaly.html. Accessed 18 April.
6. Rees G. British Dietetic Association. Folic Acid. Available from: www.bda.uk.com/foodfacts/folic_acid. Accessed: 14 November 2019.
7. Wright A, Dainty J, Finglas P. Folic acid metabolism in human subjects revisited: potential implications for proposed mandatory folic acid fortification in the UK. Br J Nutr. 2007;98:667-75.
8. Imbard A, Benoist J, Blom H. Neural Tube Defects, Folic Acid and Methylation. Int J Environ Res Public Health. 2013;10:4352-4389.
9. Stover P. Physiology of Folate and Vitamin B12 in Health and Disease. Nutri. Rev. 2004;62:S3-12.
10. Gregory J. Case Study: Folate Bioavailability. J Nutr. 2001;131:1376S-82.
11. Finkelstein J. Metabolic regulatory properties of S-adenosylmethionine and S-adenosylhomocysteine. Clin Chem Lab Med. 2007;45:1694-9.
12. Zhao W, et al. Neural tube defects and maternal biomarkers of folate, homocysteine, and glutathione metabolism. Birth Defects Res A Clin Mol Teratol. 2006;76:230-236.
13. Mills J, et al. Homocysteine and Neural Tube Defects. J Nutr. 1996;126:756S-60.
14. Afman L, et al. Homocysteine interference in neurulation: A chick embryo model. Birth Defects Res A Clin Mol Teratol. 2003;67:421-428.
15. Gest T. University of Michigan Medical School. Nervous System. Available from: www.med.umich.edu/lrc/coursepages/m1/embryology/embryo/08nervoussytem.htm. Accessed 14 November 2019.
16. Molloy A, et al. Maternal serum folate and vitamin B12 concentrations in pregnancies associated with neural tube defects. Arch Dis Child. 1985;60:660-65.
17. Viswanathan, M et al. Folic Acid Supplementation for the Prevention of Neural Tube Defects. JAMA. 2017;317:190.
18. Peake, J et al. Maternal ethnicity and the prevalence of British pregnancies affected by neural tube defects. Birth Defects Research. 2021.
19. Limb M. Flour to be fortified with folic acid within weeks. BMJ. 2018;363:4348.
20. Sweeney M, McPartlin J, Scott J. Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health. 2007;7(1).
21. Kim Y. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? Gut, 2006;55:1387-1389.
22. Kim, Y. Folic Acid Supplementation and Cancer Risk: Point. Cancer Epidemiology Biomarkers & Prevention, 2008;17:2220-2225.
23. Figueiredo J, et al. 2011. Folic acid and prevention of colorectal adenomas: A combined analysis of randomized clinical trials. International Journal of Cancer. 2011:129;192-203.
24. Butterworth C, et al. Oral folic acid supplementation for cervical dysplasia: A clinical intervention trial. American Journal of Obstetrics and Gynecology, 1992:166;803-809.
25. Childers JM, et al. Chemoprevention of cervical cancer with folic acid: a phase III Southwest Oncology Group Intergroup study. Cancer Epidemiol Biomarkers Prev. 1995;4:155-159.
26. Kennedy D, Koren, G. Identifying women who might benefit from higher doses of folic acid in pregnancy. Canadian family physician Medecin de famille canadien. 2012;58:394–397.
27. Figueiredo J, et al. 2011. Folic acid and prevention of colorectal adenomas: A combined analysis of randomized clinical trials. International Journal of Cancer. 2011:129;192-203.
28. Wald N, et al. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Medical Research Council Vitamin Study Research Group. Lancet. 1991;338(8760):131–7.
29. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832–5.
30. Tsang B, et al. Public and Private Sector Dynamics in Scaling Up Rice Fortification. Food and Nutrition Bulletin, 2016;37(3):317-328.
31. Botto L, et al. Neural-Tube Defects. New England Journal of Medicine, 1999;341(20):1509-1519.

News

New antibiotics effective against resistant bacteria

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Abstract

New antibiotics that use a two-pronged approach to kill bacteria have been discovered. These dual-acting antibiotics attack a key pathway, the methyl-D-erythritol phosphate pathway, within the bacteria via enzyme inhibition. This leads not only to essential disruption of processes within the bacterium (e.g., respiration), but also causes a build-up of pathogen-associated molecular patterns. The increased presence of these molecular pathogens leads to a more pronounced immune response to the pathogen. By utilising two methods of attack, this type of antibiotic is more than twice as effective at killing some resistant strains of bacteria compared to regular, world-class antibiotics.

Abbreviations

DAIA - Dual-acting immune-antibiotics
IspH - 4-Hydroxy-3-methylbut-2-enly diphosphate reductase
S - Svedberg units

Introduction

Antibiotics kill bacteria by acting on processes such as cell wall synthesis or DNA replication. Disrupting these processes leads to cell death by causing structural damage or preventing RNA synthesis.[1] Their discovery revolutionised healthcare, improving the survivability of infections like bronchitis,[2] increasing life expectancy substantially.[3] Bacteria can become resistant by preventing an antibiotic acting on it via a genetic mutation or gaining new DNA. An example is tetracycline, which stops protein synthesis in target bacteria by binding to the 30s subunit of the ribosome, preventing RNA interacting with it, therefore, preventing new amino acids being added to the protein chain.[4] Strains resistant to tetracycline arise due to genes like tetM. This gene creates a protein which allows the ribosome to interact with transfer RNA in a stable manner despite the presence of tetracycline.[5] **Figure 1** shows how a bacteria cell could become resistant to tetracycline. Significant resistant strains include penicillin-resistant Staphylococcus which causes pneumonia and vancomycin-resistant Enterococci. More dangerously, superbugs (bacteria which have developed resistance to nearly all antibiotics in use) can emerge. Infections from resistant bacteria cause at least 35,000 deaths a year in the US.[6] By 2050, early deaths due to antibiotic resistance are set to swell to 10 million each year;[7] clearly this crisis could have devastating impacts.

The new class of antibiotic

The Witstar Institute has made a new discovery to help target resistant bacteria, which harnesses a two-front approach and works in conjunction with the host's immune system. The presence of pathogens leads to antigen presenting via antigen presenting cells, causing T cell responses which help kill bacteria. The T-cells instigate microptosis (programmed bacteria death) within the cell by conveying granzymes within the bacterium which disrupt essential processes.[8] The Wistar Institute has harnessed this process as well as antibiotic action via dual-acting immune-antibiotics (DAIAs) to kill bacteria. Firstly, the DAIA attacks the bacteria on an essential bacterial pathway absent in humans: the methyl-D-erythritol phosphate pathway. Within this pathway it inhibits key enzymes: IspH producing terpenoids. These chemicals have essential involvement in processes like respiration and cell wall synthesis. The second prong of attack acts via the immune system. Enzyme inhibition by the DAIAs has a secondary impact: it causes a build-up of pathogen-associated molecular patterns, making the bacteria more visible to the immune system. This causes T cells to multiply and create proteins like granzymes which kill the bacterium. The action of DAIAs is shown in **Figure 2**. After testing this approach on drug resistant bacteria derivatives of cholera and pneumonia a lower dose of this drug is needed to prevent the growth of 90% of the bacteria in a colony compared to world class antibiotics. In vitro, the DAIA can leave less than half the number of cholera bacteria than current antibiotics, such as cefepime. Clearly, this antibiotic could be very effective.

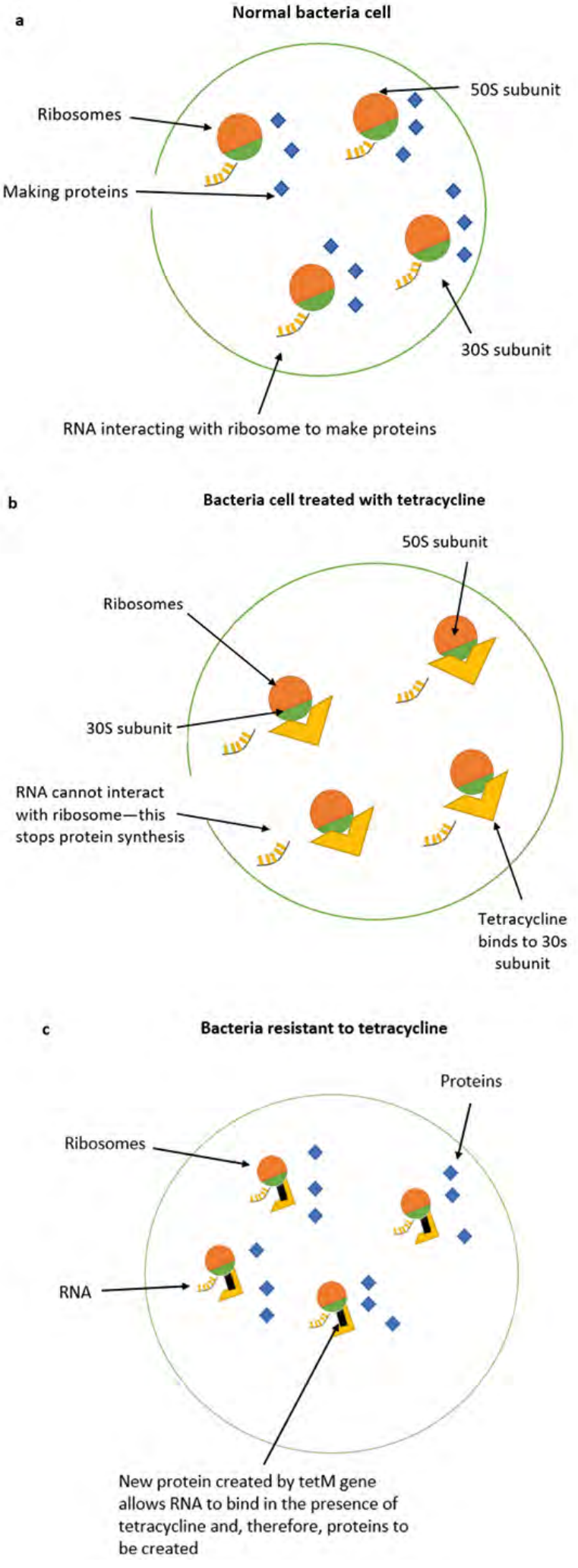

Figure 1. Illustration of (a) how a normal bacteria cell functions and produces proteins, (b) how this is stopped in the presence of the antibiotic tetracycline and (c) how bacteria cells could become resistant to the antibiotic.

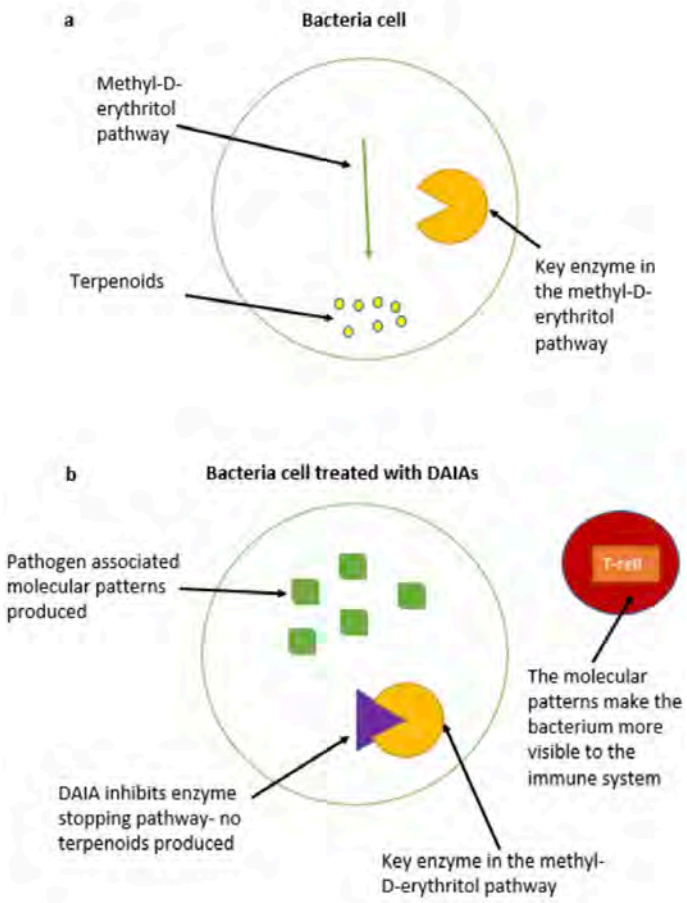

Figure 2. (a) The normal functioning of the methyl-D-ethythritol pathway in bacteria cells and (b) how this changes when cells are treated with DAIAs.

For 9 out of the 11 new antibiotics approved between 2017 and 2020 it is very likely that bacteria will quickly become resistant to them. This is because they are derived from existing classes of antibiotic where resistance mechanisms are established.[9] Cefiderocol was one of the new antibiotics approved. It is effective against strains of multi drug resistant bacteria, acting by inhibiting penicillin-binding proteins and preventing cell wall synthesis thus causing the death of the bacteria. However, scientists have discovered resistance to cefiderocol.[10] DAIAs attack bacteria on two fronts, via the immune system and the methyl-D-erythritol pathway which should make it more difficult for bacteria to develop resistance. Furthermore, there is a reduced chance bacteria have evolved to become resistant to this antibiotic due to the fact IspH inhibitors haven't yet been discovered in microorganisms, meaning bacteria haven't evolved to live without this pathway.[8] However, in my opinion, if T-cell action is an integral part of this antibiotic, individuals who have immunodeficiencies and consequently a depleted number of T-cells may struggle to produce a pronounced immune response to attack the bacteria.

There are some other dual acting antibiotics in development, however they consist of two antibiotics joined into one compound. An example is the rifamycin-quinolone hybrid. It attacks the bacteria using combined effects of both antibiotics, inhibiting RNA polymerase and activity against DNA gyrase and DNA topoisomerase, respectively. In studies it has demonstrated activity against pathogens like staphylococcus, including resistant populations. The antibiotic kills via quinolone effects against pathogens that are resistant to rifamycin, but with decreased efficacy at higher concentrations.[11] This is different to the DAIAs as, if bacteria become resistant and prevent enzyme inhibition neither the direct killing nor the immune response would occur because they both occur due to enzyme inhibition. However, when using two antibiotics there is the risk pathogens will become resistant to both.

Conclusion

The discovery of these new antibiotics is very promising, in that they could treat infections of resistant strains of bacteria. However, to keep these new antibiotics as viable weapons in the arsenal against antimicrobial resistance, their use will have to be controlled to reduce risk of bacteria acquiring mutations and becoming resistant to them.

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

References

1. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol. 2010;8(6):423-435.
2. The Oxford Scientist (2020). How the discovery of penicillin has influenced modern medicine. Available from: https://oxsci.org/how-the-discovery-of-penicillin-has-influenced-modern-medicine/#:~:text=The%20discovery%20of%20penicillin%20changed,threatening%20were%20now%20easily%20treated. Accessed: 5 September 2021.
3. Hutchings M, Truman A, Wilkinson B. Antibiotics: past, present and future. Current Opinion in Microbiology, 2019;51:72-80.
4. Scientific American (2006). How do antibiotics kill bacteria but not human cells? Available from: www.scientificamerican.com/article/how-do-antibiotics-kill-b/. Accessed: 5 September 2021.
5. Opal SM, Pop-Vicas A (2015) Molecular Mechanisms of Antibiotic Resistance in Bacteria. In: Bennett JE, Dolin R, Blaser MJ (eds) Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th edn. Elsevier Saunders, Philadelphia, PA.
6. Centres for Disease Control and Prevention (2019). Biggest Threats and Data. Available from: www.cdc.gov/drugresistance/biggest-threats.html. Accessed: 5 September 2021.
7. King A (2014). Antibiotic Resistance will kill 300 million People by 2050. Available from: www.scientificamerican.com/article/antibiotic-resistance-will-kill-300-million-people-by-2050/. Accessed: 5 September 2021.
8. Singh KS, Sharma R, Reddy PAN, et al. IspH inhibitors kill Gram-negative bacteria and mobilize immune clearance. Nature, 2021; 589:597–602.
9. World Health Organization (2021). 2020 Antibacterial Agents in Clinical and Preclinical development: an overview and analysis. Available from: www.who.int/publications/i/item/9789240021303. Accessed: 5 September 2021.
10. Choby J, Ozturk T, Satola S, et al. Widespread cefiderocol heteroresistance in carbapenem-resistant Gram-negative pathogens. The Lancet Infectious Diseases, 2021; 21(5):597-589.
11. Robertson G, Bonventre E, Doyle T, et al. Development of a Dual-Acting Antibacterial Agent (TNP-2092) for the Treatment of Persistent Bacterial Infections. Journal of Medicinal Chemistry, 2008; 52(7):2324-2334..

News

Dr Giovanni Biglino - An interdisciplinary approach to cardiovascular research

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Introduction

Dr Giovanni Biglino is a biomedical engineer with a specialisation in the field of cardiovascular research. He utilises an interdisciplinary and collaborative approach to his research and combines his knowledge of 3D modelling and passion for the arts to explore innovative concepts. Dr Biglino studied his biomedical engineering degree at Imperial College London before obtaining his PhD in cardiovascular mechanics at Brunel Institute for Bioengineering.

What research projects have you been working on recently?

I would say there are three areas to my research that I am focusing on. The first is 3D modelling work; specifically what interests me is the use of 3D technologies for communication purposes, for example, between doctor and patient. The second is broadly image analysis but especially deriving biomarkers of cardiac function from imaging data. I've been looking into this specifically using wave intensity analysis; this was an analysis introduced by one of my professors at Imperial, which I began learning during my PhD. The third area is more interdisciplinary work, collaborating with artists, musicians and scholars from other disciplines, with a strong component of patient involvement and public engagement. I've been doing a lot of work on that in the last six years; it's an area that I feel I can bring something original to. It involves more cross-sector work on the use of models to express and listen to patients' stories.

Did you have any great influen es or mentors to get into research?

Yes, definitely, I think mentoring is such a key concept.

> *I think I've had influences from very early on because I come from a very academic family. So, for me, it was very natural to be exposed to a certain way of thinking or a certain way of dissecting a problem.*

Throughout my career, there have been a few key people who have been instrumental at different stages. One person was my Head of Department at Imperial. I was coming from a very different academic background to other students in the field, and I was probably not qualified to be on the course that I was on, but years later he said to me "I wanted to give you that chance". I realised how big of a role he played in my career without me even knowing it at the time by opening that door to opportunity for me.

I also learnt a lot from my mentor during my fellowship, being exposed to his way of thinking. There was a clarity, a simplicity to it that I always found inspiring. So, I suppose it wasn't mentoring, it was more role modelling, as I admired his way of working and leadership

style. The role of a mentor is something I've come to appreciate more recently. My mentor through the mentoring program at the Academy of Medical Sciences showed me that mentoring is not just about giving advice but more about providing direction and looking at the bigger picture. I have learnt so much just by listening to her.

What do you feel are your greatest research accomplishments?

When you think about this, what's interesting is that it depends on how you define accomplishment. Because selfishly, there are pieces of work that I feel are accomplishments because of how I worked on them. But, if you think of accomplishments in terms of impact, in this context patient impact, there's one project which comes to mind: it was a piece of work that culminated in a national exhibition called "The Heart of the Matter". It was a project about technology and art representing stories of patients with heart disease, and it was presented in different venues across the country.

I say this was an accomplishment not just because of the size of the project but because feedback revealed that visitors (including patients) had been inspired by the piece, whether taking new initiatives in their lives or seeing their children's journey in a different way.

What qualities do you think make a good researcher?

I do think there are some common qualities amongst good researchers:

- The first is open-mindedness—always go in with an open mind.

> *• Curiosity also undoubtedly, as it doesn't matter what field you are in, curiosity is often what drives trying a different approach, experimenting with a new technique, reading somebody's work, whatever it is. I think curiosity is integral.*

- Something else is probably patience, which is something that I don't have! It was very counterintuitive for me to choose research as a profession because I'm so impatient by nature. Patience is something I've had to learn because research is not something where you have a quick reward. It can take a couple of years to polish a paper and get it accepted, being rigorous takes patience, good quality research takes time, but in the end the outcome is better because of that.

Any advice for students who would like to get into research?

I have often observed that good researchers that I've met have created their own niche, whatever that may be—whether it's a method, specialising in a topic, tackling a problem in a new way, sometimes it's about leveraging things that are specific to you. Whereas we sometimes counterintuitively privilege other things in research because we think that's what we should be doing, which is not always be a good thing. Of course, in some things there are rules that need to be followed, but as you progress it's about realising "what is it that I bring?".

> *What you bring creates your niche. If you pay attention to your niche, you may get more out of it and contribute more to research.*

Contribution statement The author of this work was solely responsible for the conception of the piece, conducting the interview and drafting and editing the manuscript. Both the author and interviewee gave permission for inclusion in Inspire.

Education & Teaching

Student perspectives on the benefits of interprofessional education experiences

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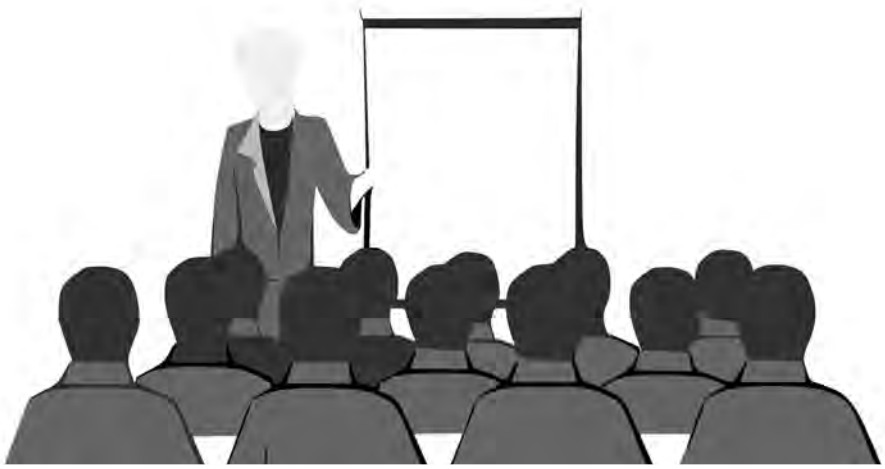

Abstract

Aims Investigate the impact of interprofessional education (IPE) experiences on third-year dental students after undertaking projects with students from the following allied health professions: Adult Nursing, Childhood Nursing, Dietetics, Speech and Language Therapy and Midwifery.

Methods 56 third year dental students undertook the interprofessional engagement module and were asked to complete the Interprofessional Collaborative Competencies Attainment Survey (ICCAS) questionnaire. 55 students returned the form and 45 of the forms were completed fully. The mean pre- and post-participation scores from students for each ICCAS subscale were analysed.

Results All subscales demonstrated a self-reported increase in perceived competency, with the largest increases being reported for 'Collaboration'. Overall, ICCAS scores showed a statistically significant increase between pre- and post-participation ratings (p<0.001).

Conclusions Students reported an increased understanding of the roles of other healthcare professions that can promote a collaborative approach in their future careers. The feedback completed by dental students at Peninsula Dental School is a marker of the potential of IPE and its importance within undergraduate dental education. The limited number of participants and dissimilar IPE projects within groups is a limitation of this study; however the unequivocal positive response highlights that all students were able to gain considerably from IPE.

Abbreviations

ANOVA - Analysis of variance
BDS - Bachelor of Dental Surgery
GDC - General Dental Council
ICCAS - Interprofessional Collaborative Competencies Attainment Survey
IPE - Interprofessional education
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
WHO - World Health Organization

Introduction

Dental students in their 3rd year of a 5-year Bachelor of Dental Surgery (BDS) undergraduate degree at Peninsula Dental School, University of Plymouth, undertake an interprofessional engagement module. The module learning outcomes aim to ensure students are able to take responsibility for establishing networks with health professionals and other relevant individuals and organisations, recognise the responsibilities of a dentist as an access point to and from wider healthcare and communicate the importance of oral health to other healthcare professionals.

> *Interprofessional education (IPE) is described as a learning opportunity where 'students from two or more professions learn about, from and with each other to enable effective collaboration and improve health outcomes'.*[1]

Incorporation of students from various healthcare courses within this type of teaching initiative has shown to positively influence communication between the professions and the understanding of each other's roles.[2] With regards to its impact on patient care, it has demonstrated improved health outcomes[3] as well as higher levels of satisfaction reported by patients.[1] The long-term benefits of IPE are

particularly relevant during the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, which has demonstrated the need for collaboration between healthcare workers to manage the crisis. Further to this, the dental workforce has changing demands, with an increasing ageing population that presents older patients with complex medical conditions. This has led to an increase in need for dental treatment to be carried out as part of a multidisciplinary team.[4]

Third-year BDS students have worked in small groups alongside students from different health professions to develop student-led projects designed to improve knowledge of the impact of poor oral health in other healthcare professions, learn about the role and scope of practice of allied health professions and encourage interprofessional working to improve patient care once graduated. The professions the dental students worked alongside included dietetics, adult nursing, childhood nursing, midwifery and speech and language therapy. During the projects, dental students worked closely with the other healthcare professionals to share working practices and understand how the needs and demands of different populations were managed. The dental students assessed the training in dental and oral health care provided to healthcare colleagues and worked to explore the relationships between general health and oral health, including the impact other healthcare professionals can make in supporting improvements in oral health. Examples of projects undertaken included recommending curriculum opportunities appropriate to the identified needs and demands of patients and their healthcare team, working on case studies to understand opposing viewpoints, attending presentations by allied healthcare professionals explaining their role and topics of relevance to their patients, and dental students delivering teaching events on topics relevant to oral health.

Following completion of the module, students were asked to complete the Interprofessional Collaborative Competencies Attainment Survey (ICCAS)[5] questionnaire. This is a validated tool to self-report changes in interprofessional care competencies. The questionnaire was provided to students and recorded pre- and post-participation in IPE activities. The aim of this study was to analyse the perspective of dental students on the benefits and any improvement in their interprofessional care competencies after participating in interprofessional activities and engaging with students from different allied health professions.

Methods

Participants The sample was comprised of 3rd year dental students who would be completing the IPE module which is a mandatory requirement for successful completion of the course. The 2019/20 cohort of third year BDS included 56 students; 26 male, 30 female, of which 20 self-identified as Asian, 25 as White, and 10 as Other (1 student did not volunteer this information at enrolment). All undertook the IPE module, and all were asked to complete the ICCAS as part of this evaluation. 55 students returned forms, of which 45 had fully completed ICCAS forms. Only complete ICCAS returns were analysed. The ICCAS questionnaire does not collect respondent data regarding demographics, so we have not included any analysis of responses by demographic subgroup.

Of the 45 BDS students for whom data was analysed, 5 worked with Adult Nursing students, 10 with Childhood Nursing students, 11 with Dietetic students, 6 with Midwifery students, and 13 with Speech and Language Therapy students.

Design and analysis Students undertaking the IPE module completed the ICCAS form immediately following the completion of their IPE project to record their experiences of integrated learning. The ICCAS comprises 20 Likert-scale items which participants use to indicate their agreement with statements related to elements of IPE such as active listening, describing abilities and contributions to teamwork, and addressing team conflicts. Each statement is responded to for 'Before participating' and 'After participating'. Items are grouped into subscales for 'Communication' (ability to communicate effectively in a team), 'Collaboration' (ability to collaborate effectively), 'Roles and responsibilities' (understanding their own and others' roles and responsibilities within the team), 'Collaborative Approaches' (ability to utilise an inter-professional, integrated approach to decision-making and care), 'Conflict Management' (ability to address conflict respectfully and constructively), and 'Team Functioning' (ability to function effectively as a team with respect to the scenario goals).

In addition to completing the ICCAS, participants were also asked to record the profession of the students with which they worked on their projects.

To evaluate ICCAS scores by time, subscale, and the professions paired for the IPE project, scores were compared using a 2 Time (Pre, Post) by 6 (Subscales) by 5 (profession worked with) repeated measures analysis of variance (ANOVA). Repeated measures t-tests were also conducted for each subscale of the ICCAS as planned post-hoc evaluations of the statistical significance of differences between students' pre- and post-project responses.

Results

Table 1 shows the mean pre- and post-participation scores from students for each ICCAS subscale, along with the standard deviation of Likert responses and mean change between pre- and post-participation ratings. All subscales show a self-reported increase in perceived competency, with the largest increases being reported for Collaboration, adopting a patient centred approach, and overall team functioning.

Table 1. Overall ICCAS scores by subscale and time, including the mean change in subscale score.

Subscale	Pre		Post		Mean Change*
	Mean	SD	Mean	SD	
Communication	4.92	1.03	5.93	0.97	1.02
Collaboration	4.53	1.29	5.86	1.10	1.33
Roles and responsibilities	5.08	1.16	6.14	0.75	1.06
Patient centred approach	4.54	1.21	5.88	0.98	1.34
Conflict management	5.29	1.10	6.14	1.05	0.84
Team functioning	4.62	1.30	5.82	1.06	1.20

n=45; incomplete ICCAS forms were excluded from the analyses
*All pre-post mean changes were statistically significant at $p<0.001$, as tested by repeated measures t-tests

Comparison of subscale scores across time and different professions 'worked with' using a 2 Time (Pre, Post) by 6 (Subscales) by 5 Profession (profession worked with) repeated measures ANOVA revealed that overall, ICCAS scores showed a statistically significant increase between pre- and post-participation ratings ($p<0.001$). Whilst these increases vary from 0.84 for conflict management to 1.34 for patient centred approach, all subscale increases were found to be statistically significant at $p<0.001$ using repeated-measures t-tests.

Whilst overall ICCAS scores increased between pre- and post-participation ratings, there were differences in the amount of

increase between profession pairings, as shown in **Figure 1**. Primarily, all profession pairings showed an increase in ICCAS scores, except where BDS students were paired with Adult Nursing students.

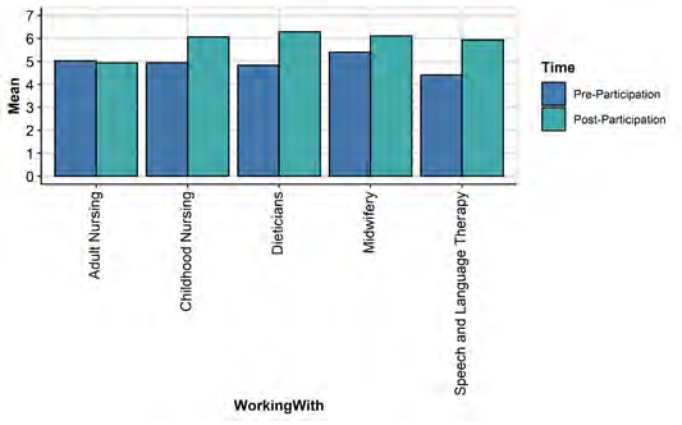

Figure 1. Overall mean pre- and post-participation ICCAS ratings by the professions BDS students worked with.

When considering these results by subscale, it appears that when paired with Adult Nursing students, BDS students' ratings of scores on items related to 'Roles and Responsibilities' (understanding their own and others' roles and responsibilities in a task) and 'Team Functioning' (ability to work effectively as part of a team) capabilities showed an increase. But there was a reduction in all other subscales. This contrasts with BDS students paired with any other profession, who all showed increased ratings across all subscales (**Figure 2**).

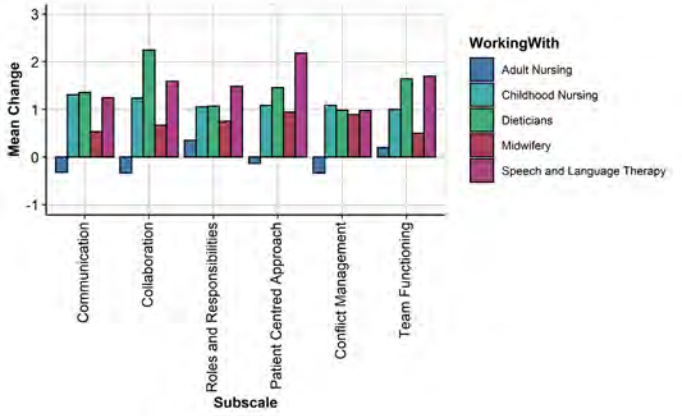

Figure 2. Mean change (post-pre) in ICCAS ratings by subscale, by the profession BDS students worked with.

Discussion

The results of our study displayed an increase in ICCAS ratings, highlighting improvement in all areas and outcome measures following IPE.

> *Students undertaking the ICCAS questionnaire consistently self reported higher aptitude in collaborative competencies after their respective IPE projects had been completed compared to the start of the IPE module.*

Strengths and limitations It is recognised that a limitation of this study is the self-reporting of collaborative working skills. As the module was assessed, students may have been biased towards marking themselves more highly post module in the self-assessment process, however the self-assessment marks did not contribute to their grade in the module. Although the module was compulsory, participation in the study was voluntary and yet a high number of students completed the ICCAS forms. In addition, as projects were student-led, there was considerable heterogeneity between the interventions that followed, leading to varying experiences of the students that undertook them. However, the projects were based upon common learning outcomes, provided by the faculty, that ensured the students had a framework to plan their intervention and required the completion of a graded piece of reflection after the intervention. The provision of such guidance and summative assessment at the end of the project have been identified as key components of an 'ideal intervention' which are important for it to be effective.[6] Due to the relatively small size of the year group, the number of BDS students in the study was sufficient for evaluation when all groups are put together. But upon division to the individual groups in which the students worked, the sample size is likely to be too small for detailed analysis of the experience within each group of healthcare profession students. However, as the IPE module continues to be an integral part of the BDS degree at the University of Plymouth, we hope to carry out similar research using higher numbers of participants.

Despite these factors, many features of this project strengthen its findings. Firstly, the ICCAS questionnaire is a validated tool used to assess the changes in interprofessional collaboration because of IPE competencies. It is short and easy to understand and administer.[7] This would ideally prevent misinterpretations by individuals and exemplifies a sound base to record results. Further to this, the response rate of the participants was high and so representative of the cohort.

The overall trend of improved collaborative working competencies across all groups indicates better perceptions of each other's roles between the different groups. It is suggested that IPE experience may lead to better interprofessional working relationships after graduation as students begin to appreciate the importance of interprofessional collaboration.

Study outcomes The organisation of the interprofessional module at Peninsula Dental School has been designed in a way which maximises the benefits for students. Specific examples of this include common learning outcomes for all students, group presentations by students for the rest of the cohort on their experiences followed by feedback from a panel, and a written reflective assessment which is marked on specific criteria that the students are aware of this. All of these have been identified as indicators of good IPE activities by the World Health Organisation (WHO). The WHO also appreciates that effective IPE relies on expected outcomes and an assessment of what has been learnt.[1]

Our study also aligns with previous findings and literature. Research on the effectiveness of IPE has previously been completed, using the same ICCAS tool, with students from medicine, dentistry, midwifery and nursing practitioner courses. This study found that students self-reported an increased understanding of each other's roles, and IPE fostered better communication as well as effective patient management.[8] Moreover, the research at Peninsula Dental School has gone one step further by engaging dental students with students from healthcare professions which they may not otherwise correspond with directly to enhance management of patients. This process has highlighted the key role played by these professionals when non-dental aspects of the health needs of patients require addressing, to improve the overall prognosis of dental treatment. An example of this includes speech and language therapy professions that are essential when conditions, such as cleft lip and palate, may compromise oral health by hampering oral hygiene and nutrition because of missing or malformed teeth. Likewise, the importance of dieticians is clear when managing patients with conditions such as diabetes, as the close association between diabetes and oral health, including their adverse effects on each other if poorly managed, is well reported.[9] IPE can allow a multidisciplinary team to work in

integration with the shared goal of improving oral and general health.[10]

Conclusions

> *Presently, there is a great need for interprofessional collaboration due to demands on the dental workforce, including an increasing ageing population, emphasis towards preventive management and the introduction of managed clinical networks.*[11]

The General Dental Council (GDC) also emphasises that an early opportunity in training allows potential registrants to recognise the link between good quality teamwork and quality of care provided. Therefore, interprofessional activities prior to qualification may allow students to enter the workplace better equipped but also feeling reassured that though they may be working in a single surgery, they are part of a wider network of professionals who they can approach and are able to bolster patient management and improve treatment outcomes.

The feedback completed by dental students at Peninsula Dental School is a marker of the potential of IPE and its importance within undergraduate dental education. The limited number of participants and dissimilar projects within groups is a limitation of this study, however the unequivocal positive response highlights that all students were able to gain collaborative skills as well as understanding of the professions they worked alongside through this module. Nonetheless, it is our aim to carry out further investigation using larger cohorts and bigger sample sizes to support these findings in the future.

IPE allows dental students to think outside of the curriculum of their BDS degree and appreciate that in order to work in the patient's best interests, they must be able to treat them holistically by taking all aspects of their health into consideration. The interaction with students from a multitude of healthcare professions widens this view by putting into perspective how oral and general health are synergistic. The initiative also challenges stereotypical perceptions of different healthcare groups and fosters a team-led approach to patient management. A collective approach to care can establish a supportive network for the patient, lead to patient-centred management plans and, ultimately, improved treatment outcomes.

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References

1. World Health Organisation (2010). Framework For Action on Interprofessional Education & Collaborative Practice. Available from http://apps.who.int/iris/bitstream/handle/10665/70185/WHO_HRH_HPN_10.3_eng.pdf;jsessionid=8B44ED8C299532BA1218068CECB3A425?sequence=1. Accessed 2 February 2021.
2. Haber J, Hartnett E, Allen K, et al. The Impact of Oral-Systemic Health on Advancing Interprofessional Education Outcomes. Journal of Dental Education. 2017;81(2):140-148.
3. Remington T, Foulk M, Williams B. Evaluation of Evidence for Interprofessional Education. American Journal of Pharmaceutical Education. 2006;70(3); 1-7.
4. Coleman A, Finn G, Nattress B. Interprofessional education in dentistry. British Dental Journal. 2018;225(3); 257-262.
5. Archibald D, Trumpower D, MacDonald CJ. Validation of the interprofessional collaborative competency attainment survey (ICCAS). J Interprof care 2014; 1820:1-6
6. Buring S, Bhushan A, Brazeau G. Keys to Successful Implementation of Interprofessional Education: Learning Location, Faculty Development, and Curricular Themes. American Journal of Pharmaceutical Education. 2009;73(4):60
7. Schmitz C, Radosevich D, Jardine P. The Interprofessional Collaborative Competency Attainment Survey (ICCAS): A replication validation study. Journal of Interprofessional Care. 2016;31(1):28-34.
8. Haber J, Hartnett E, Allen K, et al. The Impact of Oral-Systemic Health on Advancing Interprofessional Education Outcomes. Journal of Dental Education. 2017;81(2):140-148.
9. Borgnakke W S. IDF Diabetes Atlas: Diabetes and oral health – A two-way relationship of clinical importance. Diabetes Research and Clinical Practice. 2019; 157(11):1-19.
10. Ong H, Wan C, Gao X. Interprofessional Collaboration in Addressing Diet as a Common Risk Factor: A Qualitative Study. Journal of Research in Interprofessional Practice and Education. 2015;5(2): 1-12.
11. Coleman A, Finn G, Nattress B. Interprofessional education in dentistry. British Dental Journal. 2018;225(3).

Lessons learned from conducting a virtual conference

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Abstract

This article discusses the highlights and challenges of organising and running an online conference for medical students. Furthermore, using feedback collated and literature review, this article suggests how to improve attendees' experiences, focusing on optimising attention and encouraging participation. Both organising and attending conferences are great ways to build on a student's CV. This article aims to inspire more medical students to organise online conferences and to improve the experience of attendees.

Introduction

In March 2021, we and 5 other students from Bristol, Southampton and Exeter University hosted a virtual acute care conference aimed at medical students. By outlining our experiences, we aim to inspire students to organise conferences, allowing them to enhance their leadership qualities. Furthermore, they can utilise the recommendations we have drawn from our reflections and current literature to improve the conference experience.

Why host a conference?

During the COVID-19 pandemic, students were deprived of clinical placements and gaining insight into specialties became challenging. Therefore, we conducted this event to increase awareness of career pathways and the day-to-day life of clinicians.

The conference allowed students to present posters, providing a great CV-building opportunity. For example, the first-place poster provided attendees with insight into the trajectory of COVID-19 patients post emergency-department admission. Organising a conference is a good example of leadership and shows dedication to a speciality, making it a desirable outcome during the Physician ST3 application process.

Organising a conference: the highlights and challenges

A comprehensive checklist of the organisation process can be found in **Figure 1**.

The conference had several highlights, which outlined the importance of organising such events and the challenges served as great learning points.
The highlights:

- Building a multi-institutional team
- Variety of speakers
- The feedback

Building a multi-institutional committee allowed us to work with members who had different aptitudes and experiences. This decreased the burden on each member whilst creating greater diversity within the conference committee and speakers. This variety in speakers resulted in interesting Q&A sessions, allowing for engagement and a true insight into the 'life of a clinician', something that is often confined to placements. Both these elements led to a successful conference reflected by positive feedback. Particularly our pre-clinical colleagues, who have spent most of their medical education in lockdown, felt that this conference helped them reaffirm their goals, an insight they may have lost during the pandemic (**Figure 2**).

Figure 1. Comprehensive checklist outlining the process used to organise the conference.

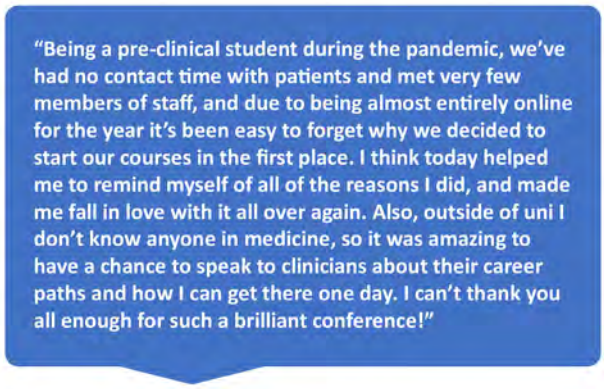

Figure 2. Feedback from an attendee about the benefits of the conference. The individual provided consent for use of data.

The challenges:

- Work–life balance
- Rejection
- Trusting technology.

Organising a conference was demanding whilst maintaining our academic responsibilities and hobbies.

> *We alleviated stress by appointing topic leads to take on positions of responsibility. We allocated jobs effectively, ensuring the speakers were found in time with consistent communication between team members.*

This communication helped us bond as we began to trust each other to work independently. Another stressor was that, unfortunately, some potential speakers turned down the offer to speak. Although understandable, this was demoralising, particularly with some clinicians dropping-out closer to the conference. We overcame this by approaching clinicians interested in teaching and pre-existing contacts of confirmed speakers. However, the greatest challenge was adapting to the technology and its interactive features. To address this, we met with colleagues who had previously held online events. While stressful, these challenges helped us become better leaders. The experience will be relevant for us as clinicians, teaching us about team building, adapting to a team and the importance of each member in reaching a goal.

Using our feedback

Collecting feedback is essential. The feedback form contained 13 questions gathering quantitative and qualitative data.
To improve the value of feedback, we believe that forms should focus on written answers, which allow participants to provide more insight. Furthermore, a focus group of volunteers could be useful to gain deeper understanding of areas that require improvement.

Two main issues were highlighted: the length of the conference and a lack of engagement. These will be discussed further below.

How long should a conference last?

One recurring theme in our feedback was that the day was too long, and attendees struggled to concentrate.

A solution to this could be to keep the same number of lectures but shorten them to 15–20-minutes, which would condense the day and allow attendees to maintain concentration.[2,3,4]

Additionally, students could choose which lectures to attend, allowing them to decide on the length of their own day. This may reduce students' attendance but would not affect the conference's overall scope. Furthermore, attendees with a pre-existing interest in a topic are more likely to find it easier to stay focused and engaged.[5] Interestingly, Bradbury found that the critical factor for student attention span is the teacher themselves, emphasising the need for engaging speakers.[2]

Figure 3. The purpose of interactive workshops in conferences.[6]

How can you optimise engagement online?

Although a virtual setting increased accessibility to our conference, our feedback highlighted that interactivity online did not equate to face-face conversation. To increase engagement, the addition of virtual workshops can be beneficial. The purpose for organising interactive workshops is seen in **Figure 3**.[6] To create a successful workshop, Fulcher *et al*. suggest points to consider, outlined in **Figure 4**.[7]

Figure 4. A plan of how to organise virtual interactive activities.[7]
We included elements of interactivity by encouraging students to ask questions during Q&A sessions and present posters. However, the posters should be accessible before the conference, allowing more in-depth discussion.

Evidence shows that participants liked using one whiteboard for everyone to brainstorm together.[6] Alternatively, small groups allow for equal participation and can be assigned randomly or based on interest. Meyer *et al*. tried both and concluded that, although time-consuming, pre-assigned groups were superior to random allocation.[8] In student conferences, attendees could be grouped according to study year or speciality of interest.

Networking is challenging online. Becerra *et al*. restyled the concept of 'speed dating' to 'speed networking'.[6] This could be adapted to our conference as we had a 50-minute lunch break, and students could be matched depending on different universities. Interaction is not obligatory and making it optional would result in productive conversation.

Conclusion

Organising a conference is an enriching experience benefitting both the attendees and organisers, creating a space for learning and interactivity, and a great project to refine leadership skills.

Although the feedback was mostly positive, we found areas for improvement. With a subsequent literature review, we believe that students organising future online conferences can make additions to enhance attendees' experiences. A pre-event questionnaire could be used to ascertain whether the attendees would like shorter talks or the ability to choose the talks they attend and if they would like to take part in networking activities. To improve interactivity, large group brainstorming tasks and pre-assigned small group sessions could take place.

Contribution statement Both authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. Both authors drafted the work or revised it critically for important intellectual content and gave final approval of the version to be included in Inspire. Richard Molyneux is the guarantor of this work.

References

1. Stalmeijer RE, Mcnaughton N, Van Mook WN. Using focus groups in medical education research: AMEE Guide No. 91. Medical teacher, 2014;36(11), 923–939.
2. Bradbury NA. Attention span during lectures: 8 seconds, 10 minutes, or more?. Advances in physiology education, 2016;40(4):509–513.
3. Cosimini MJ, Cho D, Liley F et al. Podcasting in Medical Education: How Long Should an Educational Podcast Be? Journal of graduate medical education, 2017;9(3):388–389.
4. Lortie CJ. Online conferences for better learning. Ecology and evolution, 2020;10(22):12442–12449.
5. Harackiewicz JM, Smith JL, Priniski SJ. Interest Matters: The Importance of Promoting Interest in Education. Policy insights from the behavioral and brain sciences, 2016;3(2):220–227.
6. Becerra ZM, Fereydooni N, Kun AL et al. Interactive Workshops in a Pandemic: The Real Benefits of Virtual Spaces. IEEE Pervasive Computing. 2021;20(01):35-9.
7. Fulcher MR, Bolton ML, Millican MD et al. Broadening participation in scientific conferences during the era of social distancing. Trends in microbiology. 2020;28(12):949-952.
8. Meyer MF, Ladwig R, Dugan HA et al. Virtual Growing Pains: Initial Lessons Learned from Organizing Virtual Workshops, Summits, Conferences, and Networking Events during a Global Pandemic. Limnology and Oceanography Bulletin. 2021;30(1):1-1.

Opinion

Sedentarism in children due to COVID-19

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Abstract

Non-communicable diseases (NCDs) build up the major disease burden in both developing and developed countries. Each year it causes up to 71% of deaths across the globe. The leading cause of NCDs lies in childhood practices which are encouraged by society and its socio-ecological model. The global pandemic COVID-19 has further promoted the notion of sedentary behaviour (SB) and physical inactivity. This article informs the reader about the prevalence of SB and how the pandemic has aggravated the common public health concerns. The social and physical modifications during the global health crisis will have long lasting impacts on children's physiological wellbeing and it can lead to poor health outcomes in children and adolescents. Since the COVID-19 restrictions have continued in 2021 too, it is the time to realise the sedentary patterns and promote optimal wellbeing of children and adolescents.

Abbreviations

NCD - Non-communicable disease
PA - Physical activity
PI - Physical inactivity
SB - Sedentary Behaviour
WHO - World Health Organization

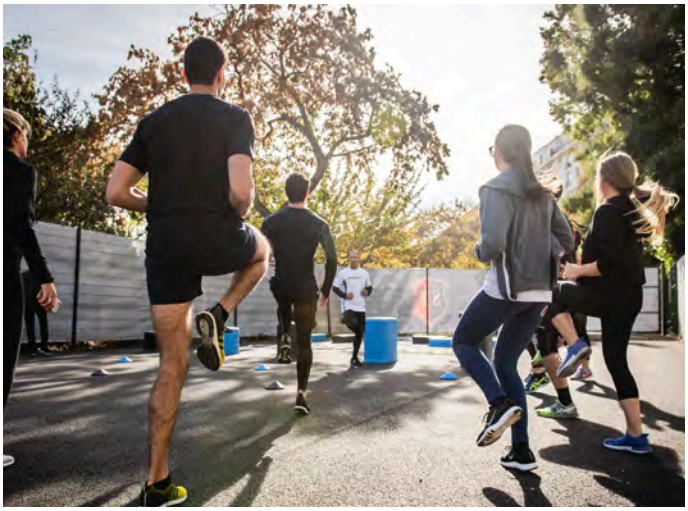
Introduction

The COVID-19 pandemic not only upended the livelihoods of many and the global economy but also brought about comprehensive lifestyle transformations. The transition of being engaged in a physical space to working and studying remotely have resulted in an increasing trend of unhealthy habits present in nearly every age group, particularly in children.

On March 11, 2020 the World Health Organization (WHO) declared COVID-19 as a global pandemic.[1] The steps taken to cease the spread of virus placed the whole world in lockdown. Although the disease tends to show low-grade symptoms in children, the sudden closure of educational institutions confined the children to their homes, which undoubtedly put their mental, physical, and social wellbeing at stake.[2] Closure of recreational centres halted the normalcy of life and put them under undue strain. While stress was prevalent among the public, there was also a factor of dealing with uncertainty regarding the future. To combat the effects of the virus, various socio-behavioral adaptations (social/physical distancing and lifestyle changes, such as online schooling) were undertaken. Though these measures reduced the infection rates across the globe they also produced some detrimental effects with regards to the social conditioning of children.[3]

Physical activity in children and adolescents

It has been emphasised by several studies that physical activity (PA) among children and adolescents plays a huge role in reducing disease burden. The foundation of many non-communicable diseases (NCDs) like hypertension, diabetes and cardiovascular diseases lies in unhealthy patterns developed during childhood. The term 'PA' is defined by any bodily movements produced by the voluntary muscles that requires energy expenditure.[4] PA is a broad concept, and it is characterised by various subtypes which include exercise, playing, working, active transportation, house chores and recreational activities. According to the WHO, the recommended levels of PA for children and youngsters is at least 60 min daily of moderate- to vigorous-intensity physical activities.[5] The health benefits associated with physical fitness are many including cardio-metabolic health, bone health, and behavioural and cognitive development. Some studies suggest that even modest amounts of PA can have tremendous health benefits in high-risk groups.[5]



Sedentary behaviours in children and adolescents

The two terms PA and sedentary behaviours (SB) are used interchangeably but, by definition, the above-mentioned terms are entirely different. The concept of a sedentary lifestyle not only ends at lack of PA, but it also includes the indulgence of low energy activities for a prolonged period of time. These activities include prolonged sitting, lying down, sleeping, and watching TV. According to a study published in the American Journal of Public Health in 1999 SB is defined as dissipating less than 150 kcal/day in moderate to high intensity activities.[6]

> *In the light of the COVID-19 pandemic, the idea of distant learning promotes greater than required sitting and screen time.*

Initial studies suggest that increased screen time among children and adolescents has promoted mindless eating and physical inactivity (PI).[7] I think the current health dilemma deals with maintaining a healthy lifestyle while avoiding SBs, whilst abiding to precautionary measures.

Recommendations

The majority of studies conducted during the COVID-19 pandemic found that the PA levels declined while SB increased regardless of the population, or the methodology used.[8] The lockdown rules are different for every region; in such circumstances we need to adapt the new policies and rules according to the community and population.

> *To enhance PA in children, promotion of digital based PA such as physical training through mobile apps is recommended.[9]*

Similarly, lessons to enhance PA through online learning should be incorporated. Exercise in the form of moderate to high intensity PA can enhance both mental and physical health. Aerobic exercises are moderate intensity workouts which pump up the heart rate quickly, are necessary for cardio-respiratory fitness, and can be done easily. Simple tasks like climbing stairs or jumping over objects, when performed in a repetitive manner can prove to be beneficial for physical health.

> *Children should also be encouraged to actively partake in outdoor activities like walking, running, and cycling.*

These activities can be performed with necessary safety measures along with local government interventions.[10]

SB can be eliminated through joint efforts of schools and community centres. Teachers should remind the whole class to take stand/walk/dance breaks for 2–5 min every 20–30 min during online learning sessions. Parents should be guided on how to break up sedentary patterns by indulging children in household chores (sweeping, dusting, mopping, washing dishes, and doing laundry).[10]

So, what kind of physical training is needed when outdoor mobility is restricted? I believe that it is not mandatory to have a perfect high intensity workout routine but what is necessary is to strike a balance between workout and leisure activities. The recommended workout during a pandemic includes aerobic exercises which also help to reduce risk of NCDs, along with muscle and bone strengthening exercises. Strengthening the muscles not only makes them stronger but it reduces the risk of future obesity too. Nevertheless, a few minutes of stretching and mobility exercises improves overall health and wellbeing.

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.

References

1. World Health Organization. (2020). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from: www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed: 25 March 2021.
2. Harvard Health Publishing (2021). Coronavirus outbreak and kids. Avialable from: www.health.harvard.edu/diseases-and-conditions/coronavirus-outbreak-and-kids. Accessed: 25 March 2021.
3. Ghosal S, Bhattacharyya R, Majumder M. Impact of complete lockdown on total infection and death rates: A hierarchical cluster analysis. Diabetes & metabolic syndrome, 2020; 14(4):707–711.
4. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public health reports, 1985; 100(2):126–131.
5. World Health Organization. (2020). Physical activity. Available from: www.who.int/news-room/fact-sheets/detail/physical-activity. Accessed: 25 March 2021.
6. Bernstein MS, Morabia A, Sloutskis D. Definition and prevalence of sedentarism in an urban population. American journal of public health, 1999;89(6):862–867.
7. Delfino LD, Dos Santos Silva DA,Tebar WR, et al.. Screen time by different devices in adolescents: association with physical inactivity domains and eating habits. The Journal of sports medicine and physical fitness, 2018;58(3):318–325.
8. Stockwell S, Trott M, Tully M, et al Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review BMJ Open Sport & Exercise Medicine 2021;7:e000960.
9. Yang Y, Koenigstorfer J. Determinants of physical activity maintenance during the Covid-19 pandemic: a focus on fitness apps. Translational Behavioral Medicine, 2020;10(4):835–842
10. Bates LC, Zieff G, Stanford K, et al. COVID-19 Impact on Behaviors across the 24-Hour Day in Children and Adolescents: Physical Activity, Sedentary Behavior, and Sleep. Children, 2020;7(9):138.

Opinions

The evolution from mechanical restraint to moral treatment in Victorian madhouses

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Abstract

In the 19th century, mental asylums (previously known as madhouses) underwent reforms to improve the quality of care for the mentally ill. Mechanical restraint was the most common form of patient management in asylums and was justified by many. William Tuke, Robert Gardiner Hill and John Conolly championed the philosophy of moral treatment and applied their practices in their own asylums. Positive results contributed to legislation resulting in humane treatment being used in novel asylums. Despite these changes, moral treatment wasn't sustainable as there was severe overcrowding, leading to poor levels of care. The rise and fall of moral treatment is argued to have paved the way for modern psychiatric treatments, yet its morality has been questioned by critics such as Michel Foucault.

Introduction

During the Victorian era, there was little understanding of mental illnesses and physical treatment was seen as the only option. Robert Gardiner Hills and John Conolly were pioneers of asylum treatment and both implemented non-restraint to control patients.[1] This new philosophy was known as moral treatment, meaning the decrease in use of mechanical restraints and implementation of less physical practices such as work therapy.[2] Allowing patients to make their own choices aided their prognosis. However, overcrowded asylums struggled to contain their patients, leading to moral treatment being phased out. This discussion will explore the failure of physical restraint in mental asylums, leading onto the rise and downfall of moral treatment.

Method

PubMed was used to collate papers on the history of moral treatment, with inclusion criteria being specific to the use of mechanical restraint and the use of moral treatment. Works published in 1967, 1983 and 1996 were used due to the lack of modern data on the matter.

Restraint

Mechanical restraint involved using straightjackets, fingerless gloves, chains, and muffs to control patients who were manic, aggressive or suicidal.[3] This restricted movement, thus decreasing harm done by patients to themselves and others. Mechanical restraints were prominent before the turn of the 19th century. However, as the century progressed, people realised the harm to patients from physical restraints such as pressure sores and nerve damage.[4]

> *The poor understanding of managing mental illnesses meant it was deemed safer to constantly restrain patients to protect themselves and others. Whilst seen by some as a necessity, other critics claimed restraints "brutalized and demoralized" patients.*[5]

Hill and Conolly championed the abolishment of mechanical restraint. By the 1840s, both had abolished mechanical restraint in their asylums. However, seclusion, also known as solitary confinement, was a practice Hill supported but Conolly opposed. Hill wrote "solitary confinement, as a means of control, may be successfully and usefully dispensed" so long as "practised attendants and vigilant superintendence" are put into place.[3] He claimed this method of treatment is as effective as mechanical restraint. However, Hill acknowledged a case regarding long term seclusion presented by his successor as house surgeon, William Smith, proving "seclusion didn't prevent violent episodes" and therefore wasn't necessary, as

patients are unpredictable.[3] The change in policy and abolishment set an example for larger asylums (e.g. Hanwell) to also practice non-restraint and non-seclusion.[3]

Moral treatment and non-restraint

Changing attitudes towards mechanical restraint allowed alternative ideas to be implemented, including work focussed on developing moral strength and rationality.

> *William Tuke paved the way for developments in treatment through founding the first hospital focussing on the healing of the mind.*[6]

Moral treatment was the combination of non-restraint and acts that activate the mind such as strenuous labour and exercise.[2]

Conolly and Hill set out to abolish all forms of mechanical restraints in asylums nationwide. Alongside the policies of non-restraint and patient surveillance, a regime of "disciplined work and exercise to stimulate the mind, tire the body and foster self-control" was implemented.[7] The Lincoln Asylum reported 647 cases of manual restraint in 1834, but by 1838, there were zero cases, supporting the argument for moral treatment.[7] However, with increasing non-restraint policies the use of seclusion also increased.

Legislation

The County Asylums Act of 1808 encouraged counties to construct asylums for those with mental illnesses. By 1827 nine overcrowded and struggling asylums had been built, with most still being housed in workhouses or prisons.[8,9] This resulted in poorer quality care for patients. The 1834 Poor Law Act stated workhouse inhabitants must be sent to newly built establishments, specific to their needs, allowing for tailored patient care. The Lunacy Act of 1890, repealed the 1808 Act and laid down the foundations for mental health legislation, making it obligatory for the county commissioners to maintain institutions for the mentally ill.[10]

Downfall of moral treatment

By the end of the 19th century the push for moral treatment failed, with overcrowding and underfunding resulting in asylums being unable to cope. From 1827 to 1930 asylum inmates increased by 635%.[11]

New forms of managing asylums were practiced, such as sedation using morphine and increased surveillance. Conolly promoted this idea, with rooms designed to promote "calming, non-punitive seclusion", with inspection plates for efficient and effective surveillance.[3]

Moral treatment was a philosophy that improved patient care and paved the way for modern psychiatric treatment. Despite this,

> *Michel Foucault criticises moral treatment as still being a form of oppression, but rather moral in nature, as opposed to the physical.*[12]

Conclusion

The fundamental change from mechanical restraint to moral treatment raised awareness of more humane methods of psychiatric care. Legislation changes improved patient care and laid down the foundation for modern day psychiatry.

Factors such as overcrowding, underfunding and inefficient asylum use led to the downfall of moral treatment. Staff were overwhelmed and resorted to mechanical or medicative restraints to regain control.

Contribution statement The author contributed substantially to the conception, design, drafting and revision of this work. The author gave final approval of this work to be included in Inspire.

References

1. Frank, JA. Non-restraint and Robert Gardiner Hill. Bull Hist Med. 1967;41(2):140–60.
2. Dunkel LM. Moral and humane: patients' libraries in early nineteenth-century American mental hospitals. Bull Med Libr Assoc. 1983;71(3):274–81.
3. Topp L. Single Rooms, Seclusion and the Non-Restraint Movement in British Asylums, 1838–1844. Soc Hist Med. 2018;1;31(4):754–73.
4. Gunawardena R, Smithard DG (2019). The Attitudes Towards the Use of Restraint and Restrictive Intervention Amongst Healthcare Staff on Acute Medical and Frailty Wards—A Brief Literature Review. Geriatrics. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6787583/
5. Science Museum (2018) A Victorian Mental Asylum (2018). Available from: https://www.sciencemuseum.org.uk/objects-and-stories/victorian-mental-asylum. Accessed: April 13, 2019
6. Porter R (1996) The Cambridge illustrated history of medicine. Cambridge University Press, Cambridge, pp 400
7. Higgs M. Life in The Victorian Hospital (2009). The History Press, Gloucestershire, pp 388
8. Unsworth, C. (1993). Law and Lunacy in Psychiatry's 'Golden Age'. Oxford Journal of Legal Studies, 13(4), 479-507. Available from: http://www.jstor.org/stable/764546. Accessed: June 7, 2021
9. Historic England. The Growth of the Asylum - a Parallel World. Available from: https://historicengland.org.uk/research/inclusive-heritage/disability-history/1832-1914/the-growth-of-the-asylum/. Accessed 16 April 2019.
10. Takabayashi A. Surviving the Lunacy Act of 1890: English Psychiatrists and Professional Development during the Early Twentieth Century. Med Hist. 2017 Apr;61(2):246–69.
11. Crossley N (2006). Contesting Psychiatry: Social Movements in Mental Health. Psychology Press, pp 244
12. Michel Foucault, Madness and Civilization: A History of Insanity in the Age of Reason (London: Tavistock, 1967), ch. 9 'The Birth of the Asylum'.

Opinion

The mental health narrative: do we need a rethink?

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Abstract

This short piece questions the current conversation and rhetoric with regards to mental health. Through inquiring into how aware we are of our mental landscapes, and whether we know where our understanding originates from, our struggle with 'not knowing' is highlighted. Additionally, the roles of neuroscience and psychiatric medications are explored by pondering if our tendency to lean too heavily on these tools may be serving to disconnect us from what manifests true wellbeing by playing on our inherent dependence on cure and treatment within medicine. Overall, the piece emphasises that areas of our lives where medicine may seem to fail us may really be traced back to our underlying priorities as a society and individually. It is suggested that the key may lie in asking honest questions in hope of a better future where wellbeing is a priority rather than a policy.

"A mind that is full of conclusions is a dead mind. A living mind is a free mind, learning, never concluding"
- Krishnamurti[1]

Over recent years we have seen a positive shift towards de-stigmatisation of our mental lives and encouragement to be more open with each other about how we feel. However, included within this shift we can observe a tendency to overlook the meaning and cause of our emotions, both on an individual and societal level. Whilst empowering us to care for each other, making mental health an entity in itself may be estranging us from calls for personal change and growth. Metaphorically speaking we may be introducing templates for our psychological lives, which see nuanced emotions through a primarily medical lens. Here lies a fine balance we must be more aware of if we are to ensure we act with peoples' best interests at heart.

One major example of this tight-rope is the thin line we walk between empowering people who are suffering—making sure they receive the help and support they need—and leading them away from the connection between these feelings and their life circumstances. Focussing purely on mental health from the viewpoint of there being a 'problem' also inadvertently introduces the idea that a 'fix' is required by others or a medication. A process of transformation and change may be very different from a fix that returns us to some concept of normal.

Even our decision to label depression as an illness, a disease or otherwise, massively dictates our approach. Labelling in this way has the potential to provide an illusion of control over something that we have taken as separate from ourselves. In reality, this could serve to alienate us from meaningful emotions, encouraging us to go *around* crises when we may be best served in the long run by going *through* them.[2]

Neuroscience and pharmaceuticals fill the space left by the unknown[3]–a space we may hugely undervalue and require more than we know–with dazzling promises of cure. Our desire to fix in this way may be turning these valuable tools into entities that can become damaging due to our over-reliance on them. There are many examples of this over-reliance. For instance, we continue to have faith in the chemical imbalance model of mental illness, despite 50 years of research failing to prove it.[4] Regardless, surely the most thought-provoking point here is that even if the chemical imbalance theory were true, it does little to explain why it has occurred. Attempting to correct this imbalance biologically could therefore be synonymous with 'trying to carry water in a sieve'.

> *Medications like anti-depressants may be a useful tool, but thinking of them as a cure perpetuates an illusion that we are powerless victims at the mercy of unassuming mental diseases.*

Perhaps, the most important part of the story here is that medicine's approach with regards to mental health is not limited most by itself but by our underlying and often unsaid views in the modern world regarding life's deepest questions. How can a society that priorities the capitalist imperatives that created it–to earn, to work and to consume–then truly seek to help us live our best lives? When a person lives in a society whose every whisper and shout encourages them to conform and allow their health and wellbeing to become needs that must be met in our 'spare time', is it so surprising that so many of us feel anxious, alone and sad?

True deep-seated introspection of this kind is surely needed. Although it may be uncomfortable to ask these kinds of questions, the answers they will give are undoubtedly what we need most to collectively live our happiest of lives. Avoiding questions like: "what brings us joy and satisfaction in life as well as enriching others?", we will only end up continually 'climbing up the signpost instead of following the road'.[5]

Conclusion

Perhaps, it is not specific actions or concepts that are needed here, but rather an admission of our human fallibility as people and healthcare professionals, giving ourselves the opportunity 'not to know'. What has been discussed are just brief examples of the impact of our assumptions and the danger of forsaking open-mindedness in order to attempt to be correct. The essence of this is what we must take forward.

Our current narrative in society and medicine with regards to mental health is criminally limited. It is a story that accentuates the 'problem' of mental health without seeking to understand cause, a story that encourages us to live with an essence of survival and a story that is being told loudest in a medical voice, which might not necessarily be helping us to live our best lives. If we can become aware of our vulnerability and this narrative in the context of our own lives and also practice medicine with it in mind, then the 'best' way forward will arise spontaneously.

If you would like to read more writing of this kind you can find my website at the following link: www.meditationswithmax.co.uk

Contribution statement The author confirms that they 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.

References

1. Krishnamurti (1973). As spoken in Public Talk 3 in Ojai, CA, USA on 14 April 1973.
2. Wells M (2019). Sitting in the Stillness: Freedom from the Personal Story. Mantra Books. Alresford.
3. Remen RN (1996). Kitchen Table Wisdom: Stories That Heal. Riverhead Books. New York City, NY.
4. Davies J (2013). CRACKED Why Psychiatry is Doing More Harm Than Good. Icon Books Ltd. London.
5. Watts A (1989). The Book: On the Taboo Against Knowing Who You Are. Reissue Edition. Vintage Books. New York City, NY.

A letter re: Chemotherapy-induced nausea and vomiting in paediatric oncology

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Abbreviations

CINV - Chemotherapy-induced nausea and vomiting
CCLG - Children's Cancer and Leukaemia Group

I read with interest the published article by Abigail Wong[1] in the *Inspire Student Health Sciences Research Journal*. The author conducted a retrospective audit to determine the extent of guideline adherence in the management of chemotherapy-induced nausea and vomiting (CINV) in paediatric oncology patients. Below are my comments regarding the article.

Firstly, 11 patients were retrospectively audited to obtain data regarding 3 sequential chemotherapy cycles (for a total of 33 cycles) during which time CINV may have developed and been managed.[1] In my opinion, this is not a sufficient sample size for any valid statistical significance to be expressed. However, I recognise the limitations of using retrospective data and appreciate this has been acknowledged in the article. It is curious to see that there has been no mention of audit selection criteria or if patients were matched to said criteria. I believe it would have been useful to state if the patients were matched for sex, age, type of cancer, ethnicity, etc. If the patients had not been matched, then it would be useful to state the rationale behind this. Ruggiero *et al*[2] claim that the difficulty in creating protocols for CINV in children is due to how a child's physiology varies based on age. In my opinion, creating protocols for each age group may prove to be an inefficient use of resources. Instead, guidelines that offer evidence-based advice whilst maintaining clinical autonomy may be more appropriate.

Secondly, the author concludes that the lack of adherence to the guidelines published by The Children's Cancer and Leukaemia Group (CCLG) increases the likelihood that a child will suffer CINV due to treatment failure.[1] I find this conclusion to be unjustified. There is no mention of the reasoning behind the prescriber's treatment (apart from the flowchart in the article)[1] or whether they were following different guidelines. Comparing the CCLG's guidelines[3] with those of the Leeds Teaching Hospitals NHS Trust,[4] there are apparent differences in the choice of anti-emetics used as well as route of administration. However, non-adherence to CCLG's guidelines does not automatically imply that local protocols are less effective.

Finally, I agree with the author that implementing teaching to prescribers would likely reduce rates of treatment failure, with the caveat that the teaching would not solely be focused on the CCLG's guidelines but also take into account local protocols.

The author of the article[1] did not disclose any conflict of interest or if there was any funding associated with the audit.

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References

1. Wong A, 2020. To what extent are guidelines adhered to in the management of chemotherapy-induced nausea and vomiting in paediatric oncology? A retrospective audit. Inspire Student Health Sciences Research Journal, 3(1),60-61.
2. Ruggiero A, Rizzo D, Catalano M, et al., 2018. Acute chemotherapy-induced nausea and vomiting in children with cancer: Still waiting for a common consensus on treatment. Journal of International Medical Research, 46(6),2149-2156.
3. Children's Cancer and Leukaemia Group (2018) CCLG guideline on the management of chemotherapy induced nausea and vomiting. Available from: www.piernetwork.org/uploads/4/7/8/1/47810883/cclg_cinv_guideline_march_2018.pdf. Accessed: 16 February 2021.
4. Leeds Teaching Hospitals NHS Trust (2019) Guideline for the Prevention and Management of Chemotherapy Induced Nausea and Vomiting in Children and Young People with Cancer. Available from: www.lhp.leedsth.nhs.uk/detail.aspx?id=3959#21. Accessed: 16 February 2021.

Review

Balloon valvuloplasty surgery for the treatment of pulmonic stenosis in the dog: is there evidence for the prophylactic use of lidocaine to prevent the complications of ventricular arrhythmias?

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Abstract

The need for balloon valvuloplasty surgery for the treatment of pulmonic stenosis in dogs has become ever-increasing with the rise of popular brachycephalic dogs, such as pugs. The aims of this review are to detail the current best method for the treatment of pulmonic stenosis and to look at the role lidocaine has in the management of ventricular arrhythmias caused by the surgery. This review also evaluates, using the current literature, whether lidocaine could be potentially preventative rather than curative regarding the treatment of ventricular arrhythmias. Evidence from human studies show lidocaine has a preventative anti-arrhythmic role during pulmonary catheterisation. Evidence from a canine study shows that lidocaine is safe to administer prophylactically and has a preventative role in ventricular arrhythmias caused by gastric dilation and volvulus. This evidence is a basis for further research regarding whether prophylactic lidocaine can prevent ventricular arrhythmias in dogs undergoing balloon catheterisation.

Abbreviations

BV - Balloon valvuloplasty
ECG - Electrocardiogram
GDV - Gastric dilation and volvulus
PS - Pulmonic stenosis

Introduction

What is pulmonic stenosis? Balloon valvuloplasty (BV) has become the gold standard for the treatment of pulmonic stenosis in dogs.[1] Pulmonic stenosis (PS) is a congenital heart condition occurring in dogs and can be described as two variants: 'Type A' and 'Type B'. Type A causes a mild thickening of the pulmonary valve and fusion of the valve leaflets (flaps that act as one-way inlets for blood).[2] Type B causes moderate to severe thickening and hypoplasia of the valve leaflets as well as hypoplasia of the annulus (part of the fibrous skeleton of the heart).[2] Both types have reduced potential space for outflow of blood from the right ventricle, causing hypertrophy of the ventricle walls. Diagnosis and typing are undertaken using electrocardiography measuring the trans-pulmonic peak pressure gradients. The most severe stenosis has a gradient of more than 80 mmHg.[3] Clinically, this presents in severe patients as a heart murmur, exercise intolerance, ascites, and lethargy.[4] Importantly, the type of stenosis affects the success of BV surgery; patients with type A stenosis have a greater improvement of clinical signs after the surgery.[5] PS occurs in many breeds with overrepresentation in French bulldogs and English bulldogs. These breeds are becoming more popular, exacerbating the problem and as a result,

> *PS now accounts for around 32.1% of canine congenital heart disease.[6]*

How is balloon valvuloplasty carried out? BV is carried out under a general anaesthetic and is non-invasive.[7] The main surgical approaches are via an incision in the jugular vein or femoral vein. The jugular vein is preferred due to the increased size and ease of use in comparison to the femoral vein. A guidewire is passed through the vein followed by a vein dilator and introducer. Once the introducer is in place, the guidewire and dilator are removed. A balloon tip catheter is then passed into the introducer and the pressures in the right ventricle and pulmonary artery are measured so that the pressure gradient across the stenosis can be calculated. The catheter is moved through the right ventricle and into the pulmonary artery so that the balloon is in the position of stenosis at the pulmonary valve. The position is confirmed by angiography. Here the balloon is inflated rapidly, held for 6 seconds, then rapidly deflated. This rapid inflation forces open the closed stenosed valve leaflets and allows improved blood flow into the pulmonary artery (**Figure 1**).[7] The pressure gradient across the valve is then remeasured to check the gradient has reduced.

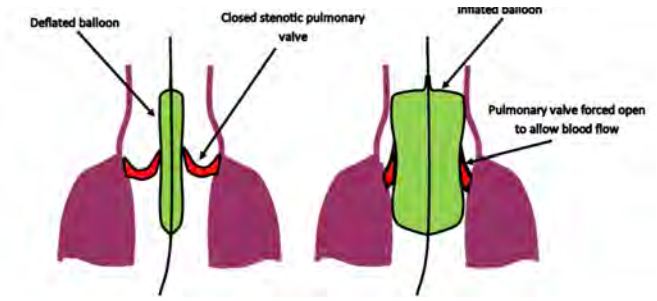

Figure 1: Balloon valvuloplasty. The left image shows the placement of the deflated balloon catheter into the pulmonary valve stenosis. The right image shows the inflation of the balloon, which stretches open the stenosis for improved blood flow out of the right ventricle. Adapted and republished, with permission, from resources at The Royal Children's Hospital, Melbourne, Australia. www.rch.org.au. Images subject to copyright.

What is the prevalence of ventricular arrhythmic complications during BV surgery and how are they currently treated? A common complication of BV surgery is the occurrence of a ventricular arrhythmia due to the endocardium of the right ventricular outflow tract being sensitive to irritation by the catheter as it passes through. Ventricular arrhythmias are monitored using an electrocardiogram (ECG) throughout the surgery. A retrospective study looking at the complications of anaesthesia in 39 dogs with severe PS undergoing BV surgery showed 54% suffered intraoperative ventricular arrhythmias.[8] Similarly, Viscacillas *et al.* (2015)[9] showed that when 46 dogs underwent BV surgery for severe PS, 87% suffered ventricular arrhythmias. In both of the retrospective studies mentioned, ventricular arrhythmias were corrected with a bolus of lidocaine. Lidocaine is an amide local anaesthetic commonly used as part of a perioperative analgesic plan, as it features a sedative effect without causing cardiovascular depression.[10] Additionally, lidocaine is an anti-arrhythmic that has long been used to treat ventricular arrhythmias in both human and veterinary medicine.[11,12] Lidocaine is a class Ib type antiarrhythmic drug and works by stabilising the membrane by blocking sodium ion channels. It therefore suppresses spontaneous depolarisation of the ventricles by a direct effect on the Purkinje fibres.[10] Currently in BV surgery in dogs, lidocaine is only ever administered should the anaesthetist detect a severe ventricular arrhythmia and treatment is usually successful. The average surgery time is 193.2 minutes and hospitalisation time is an average of 48 hours.[8] It is during this period that ventricular arrhythmias occur, are monitored, and are treated.

> *Consequentially, this is causing increased surgery and hospitalisation times and a method to prevent the ventricular arrhythmias would be advantageous.*

Methodology

A literature search was carried out using PubMed and Web of Science databases. All searches were carried out on 08/03/2021. Firstly, the PubMed search terms were: ((ventricular arrhythmia) OR (ventricular tachycardia)) AND ((lidocaine) OR (lignocaine)) AND ((prophylactic) OR (preventative) OR (CRI), where CRI=continuous rate infusion. This yielded 0 results. The search was widened by removing the focus on dogs only and by looking at catheterisation rather than specifically searching 'balloon valvuloplasty'. The term 'infarction' was excluded to narrow the search by removing arrhythmias caused by cardiac infarction which were deemed irrelevant. This yielded 9 papers, 3 of these were deemed relevant. Papers were ruled out due to irrelevance such as focusing on contrast media-induced arrhythmia or correction by laser ablation. The same search parameters were replicated in the Web of Science database as were used in PubMed. The search yielded 1 paper which overlapped with 1 of the 3 found in PubMed.

Lastly, the search was widened to look for any primary research involving the prevention of ventricular arrhythmias in dogs using lidocaine, regardless of the surgery undertaken or clinical condition. This yielded 3 papers, 1 of which was deemed relevant. Papers were ruled out due to their focus towards infarction-induced arrhythmia or the haemodynamic effects of lidocaine.

Discussion

The current evidence for the role of lidocaine to prevent ventricular arrhythmias The literature in human research regarding the preventative role of lidocaine to reduce ventricular arrhythmias during catheterisation is controversial. Sprung *et al.*[13] looked at whether lidocaine reduced the incidence of ventricular arrhythmias in patients undergoing pulmonary artery catheterisation for haemodynamic monitoring. The origin of the ventricular arrhythmias is thought to be due to the mechanical trauma of the endocardium when passing the balloon-tipped catheter through the right ventricle. This mechanical origin mirrors the cause of ventricular arrhythmias in dogs undergoing balloon valvuloplasty. The study randomly selected 31 patients from 67 to receive prophylactic lidocaine and the 36 other patients were given a placebo. The lidocaine group showed a significant improvement in the occurrence of ventricular arrhythmias compared to a placebo when catheterisation was under 20 minutes. However, no significant difference was observed when catheterisation was in place for over 20 minutes. Therefore, there is evidence of a preventative role in shorter catheterisations in humans, but this is considerably shorter than that of the time the balloon catheter is in place in dogs, as BV surgery averages 193.2 minutes in duration.[8] Another, limitation of this paper was that the patients had a systemic illness such as sepsis or respiratory failure, which may have influenced their likeliness to have ventricular arrhythmias. The efficacy of the lidocaine may then have been related to the primary illness, if the illness had a role in the cause or severity of the ventricular arrhythmias, rather than reducing the mechanical effects of the catheterisation.

Shaw *et al.*[14] looked at whether lidocaine reduced the incidence of ventricular arrhythmias in patients receiving a Swan-Ganz pulmonary catheter, which also travels via the right ventricle. The results supported the work of Sprung *et al.*, in that there was a significant reduction in the incidence of ventricular arrhythmias when prophylactic lidocaine was administered before catheterisation. Notably, no complications occurred in either study directly from the prophylactic lidocaine administration. Contrasting the evidence supporting the use of prophylactic lidocaine is the work of Salmenpera *et al.*[15]; in a double-blind comparison of prophylactic lidocaine versus saline in 107 patients, there was not a significant reduction in the occurrence of ventricular arrhythmias. However, those with catheterisation times of less than 20 minutes did have a reduced occurrence of ventricular arrhythmias, highlighting that time could be crucial in the efficacy of lidocaine and supporting Sprung *et al.*[13] where they concluded the same. It is also possible that the dosage rate of lidocaine past 20 minutes was not high enough to be at an antiarrhythmic concentration. Further concentration-dependent investigations would be valuable to address this limitation.

A study assessed whether prophylactic lidocaine in 83 dogs compared to 47 retrospective controls reduced the occurrence of ventricular arrhythmias in dogs presenting with gastric dilation and volvulus (GDV).[16] Ventricular premature complexes and ventricular tachycardia are severe complications of GDV. The dogs were treated on presentation with an intravenous lidocaine bolus followed by CRI of lidocaine and arrhythmias were monitored via ECG. The lidocaine treated group showed a 25% ($P<0.001$) reduction of ventricular arrhythmias compared to the control.

> *Therefore, lidocaine has strong evidence of being preventative for ventricular arrhythmias in dogs, though only where ventricular arrhythmias are caused secondarily due to GDV complications.*

Even though the cause of the ventricular arrhythmias is via a different mechanism to those seen in BV, lidocaine is known to treat arrhythmias by suppressing the depolarisation of the ventricles directly.[10] Therefore, the potential suppressive action may be independent of the initial cause by acting at the heart directly. Research needs to be undertaken to assess if this level of protection is present when the ventricular arrhythmias are caused by mechanical trauma.

It was concluded in this study that the prophylactic lidocaine given was not associated with any adverse effects in the dogs, though it is unclear how they distinguished the clinical signs of GDV from the side effects of lidocaine. Although, if the case, this further supports the safety of its use as a prophylactic drug in dogs. There was a significant reduction in hospitalisation time postoperatively from a median of 72 hours in the control group to 48 hours in dogs receiving lidocaine.[16] Although there was no statistical analysis of the correlation of ventricular arrhythmias and hospitalisation time, a reduction of both in the lidocaine group is a strong indicator of a relationship. The current average hospitalisation time for balloon valvuloplasty, where ventricular arrhythmias are treated at time of occurrence, is 48 hours in intensive care.[8] This is a long time in a critical state post-surgery, and it would be beneficial to research if the level of reduction of hospitalisation time seen in GDV cases could be mirrored in BV surgery with prophylactic lidocaine.

Conclusion

In summary, there is currently no primary literature evidencing the role of lidocaine to prophylactically reduce the complication of ventricular arrhythmias during BV surgery in dogs. Unfortunately, the current evidence is also limited in wider studies in dogs regarding lidocaine's preventative role. The human studies do show promising evidence, although controversial, for the preventative anti-arrhythmic role of lidocaine during pulmonary catheterisation and highlight a gap in the literature for its prophylactic use in BV surgery in dogs. Therefore, there is scope to suggest further study, with the prevention of ventricular arrhythmias already showing a positive effect in reducing hospitalisation times, as evidenced in the GDV study. Human patients are already receiving prophylactic lidocaine to reduce complications and improve welfare after pulmonary catheterisation, and with further research, there is the potential to do the same for canine patients.

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

References

1. Belanger C, Gunther-Harrington CT, Nishimura S, et al. High-pressure balloon valvuloplasty for severe pulmonary valve stenosis: a prospective observational pilot study in 25 dogs. J Vet Cardiol. 2018;20(2):115–22.
2. Oyama MA, Sisson DD, Thomas WP. Congenital heart disease. In: Ettinger SJ, Feldman EC, editors. Textbook of Veterinary Internal Medicine. 7th ed. W. B. Saunders, St Louis, MO, USA; 2010. p. 390–467.
3. Fingland RB, Bonagura JD, Myer CW. Pulmonic stenosis in the dog: 29 cases (1975-1984). J Am Vet Med Assoc. 1986;189(2):218–26.
4. Johnson MS, Martin M. Results of balloon valvuloplasty in 40 dogs with pulmonic stenosis. J Small Anim Pract [Internet]. 2004 Mar 1;45(3):148–53. Available from: https://doi.org/10.1111/j.1748-5827.2004.tb00217.x
5. Johnson MS, Martin M, Edwards D, et al. Pulmonic stenosis in dogs: Balloon dilation improves clinical outcome. J Vet Intern Med [Internet]. 2004;(18):656–62. Available from: https://doi.org/10.1111/j.1939-1676.2004.tb02602.x
6. Oliveira P, Domenech O, Silva J, et al. Retrospective review of congenital heart disease in 976 dogs. J Vet Intern Med. 2011;25(3):477–83.
7. Schrope DP. Balloon valvuloplasty of valvular pulmonic stenosis in the dog. Clin Tech Small Anim Pract. 2005;20(3):182–95.
8. Ramos R V., Monteiro-Steagall BP, Steagall PVM. Management and complications ofanaesthesia during balloon valvuloplasty for pulmonic stenosis indogs: 39 cases (2000 to 2012). J Small Anim Pract. 2014;55(4):207–12.
9. Viscasillas J, Sanchis-Mora S, Palacios C, et al. Anaesthetic management and complications of balloon valvuloplasty for pulmonic stenosis in dogs. Vet Rec. 2015 Oct;177(13):340.
10. Weinberg L. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World J Anesthesiol. 2015;4(2):17–29.
11. Anderson GA. Use of lidocaine in ventricular arrhythmias. Am Fam Physician. 1976;13(6):118–9.
12. Grossman JI, Lubow LA, Frieden J, et al. Lidocaine in Cardiac Arrhythmias. Arch Intern Med [Internet]. 1968 May 1;121(5):396–401. Available from: https://doi.org/10.1001/archinte.1968.03640050006002
13. Sprung CL, Marcial EH, Garcia AA, et al. Prophylactic use of lidocaine to prevent advanced ventricular arrhythmias during pulmonary artery catheterization. Prospective double-blind study. Am J Med. 1983;75(6):906–10.
14. Shaw TJI. The Swan—Ganz pulmonary artery catheter: Incidence of complications, with particular reference to ventricular dysrhythmias, and their prevention. Anaesthesia. 1979;
15. Salmenperá M, Peltola K, Rosenberg P. Does Prophylactic Lidocaine Control Cardiac Arrhythmias Associated with Pulmonary Artery Catheterization? Anesthesiology [Internet]. 1982 Mar 1;56(3):210–1. Available from: https://doi.org/10.1097/00000542-198203000-00011
16. Bruchim Y, Itay S, Shira BH, et al. Evaluation of lidocaine treatment on frequency of cardiac arrhythmias, acute kidney injury, and hospitalization time in dogs with gastric dilatation volvulus. J Vet Emerg Crit Care. 2012;22(4):419–27.

Review

Gut dysbiosis: does the gut microbiome affect the development of hepatic steatosis and how can this knowledge influen e future treatment?

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Abstract

There is confounding evidence to support the theory that a mutualism exists between the human body and the rich, diverse microbial community that resides within the human gut, in particular, between the microbial community and the liver. This paper will consider the influence of this 'gut-liver axis' in relation to the development of non-alcoholic fatty liver disease (NAFLD). Sources were gathered using PubMed, NICE evidence and BMJ databases, using the key search terms "(gut microbiome OR microflora) AND (non-alcoholic fatty liver disease OR NAFLD)" and "gut microbiome AND hepatic steatosis". When a gut microbiome is poorly managed, its interface with the liver is thought to have the potential to induce pathology, altering hepatic lipid metabolism and generating an excessive immune response. There are multiple mechanisms proposed in the literature regarding hepatic steatosis which will be discussed, such as the translocation of bacterial and microbial products generating inappropriate lipogenesis within the liver, and the relationship between increased body-mass index (BMI) and an overgrowth of gram-negative bacteria. This review will outline the potential utility of probiotic and prebiotic treatment to manage the composition of the microbial community and reduce states of active disease. Application of these findings in future human trials could increase our knowledge of the causes of liver steatosis and vastly improve the prevention schemes and treatment of NAFLD available in the NHS. Fundamentally, this article will consider how active management of the gut microbiome beyond diet and lifestyle changes can be altered to improve the prognosis for patients suffering from NAFLD.

Abbreviations

BMI - Body-mass index
LPS - Lipopolysaccharides
NAFLD - Non-alcoholic fatty liver disease
NLRP3- Nod-like receptor family pyrin domain containing 3
PAMP - Pathogen-associated molecular pattern
rRNA - Ribosomal RNA
SCFA - Short-chain fatty acid
TLR - Toll-like receptor
TNF-α - Tumour necrosis factor α

Introduction

The systemic interaction of the gut microbiome with the rest of the body is currently controversial and the ways in which gut microflora may be factorial in the progression of liver disease is a topic of recent debate.[1] The proposed mechanisms for how gut dysbiosis influences the development of non-alcoholic fatty liver disease (NAFLD) is in their early stages of clinical application; however, awareness of the active management of the gut microbiome through diet and lifestyle changes, alongside the role of pre and pro-biotics, is important for clinicians to consider when evaluating the causes of liver steatosis and when aiming to maximise the prognosis for patients suffering from NAFLD.[2]

The aim of this article was to determine how the contents of the gut microbiome can impact upon the pathophysiology of NAFLD.

Methodology

The search term "(gut microbiome OR microflora) AND (non-alcoholic fatty liver disease OR NAFLD)" was searched to produce the following results: BMJ 175 results, NICE 16 results, PubMed 195 results. The term "gut microbiome AND hepatic steatosis" was also used and produced: BMJ 253 results, NICE 7 results, PubMed 364 results. Of the two search terms, the former produced fewer, more relevant papers and was used preferentially over the latter search term. To elaborate, the search term "(gut microbiome OR microflora) AND (non-alcoholic fatty liver disease OR NAFLD)" produced the same list of appropriate, relevant papers found also when using the search term "gut microbiome AND hepatic steatosis", as well as additional, more recent research. Of the papers identified by the chosen primary search term, relevant papers were selected if they focussed primarily upon NAFLD and the gut microbiome, were written in English and were published within the last 15 years. In total, 25 papers were selected.

Establishing the role of the gut-liver axis in NAFLD

Within western society, NAFLD is becoming an increasing concern.[1] A global epidemiological meta-analysis studying NAFLD estimated it to be prevalent in 25.24% of the world's adult population, a figure thought to be a consequence of the increasing rates of obesity and type 2 diabetes.[2]

It is well-established that NAFLD is characterised by the elevation of pro-inflammatory markers, such as cytokines, and disturbed hepatic lipogenesis.[3] Yet, mechanisms have been proposed for the causation of liver disease as a result of gut dysbiosis and dysregulation of the intestinal microbiota.[4,5] The liver acts as an intersection between portal venous blood from the gut and peripheral organs, interacting with the microbiota-derived compounds that may pass through the gut barrier and intestinal lumen following digestion.[5] The translocation of these bacterial and microbial products has been suggested to bring about changes in metabolism in the liver and immune responses of the liver, which can lead to disease.[5]

Altered lipid metabolism and NAFLD

Many studies have questioned the relevance of genetic variation within the microbiome in relation to the pathogenesis of obesity.[7] Statistical homogeneity can be seen in results from studies using mouse models, where there is a noteworthy increase in the Firmicutes:Bacteroidetes phyla ratio in the gut microbiome of obese mice compared to lean mice.[7]

A 2008 study looking at the metagenomics of gut flora in mouse models suggested that Firmicutes dominance within obese-associated bacterial cultures results in a larger capacity for fermenting polysaccharides, a compound metabolised by the microbiome into monosaccharides and short-chain fatty acids (SCFAs).[8] These SCFAs are eventually converted to complex lipids within the liver and are likely to contribute to substantial fat accumulation and steatosis.[2,7,8] Transplantation of these microbial samples to the gut of healthy mice has proven to induce an obese phenotype, suggesting that

> *the genetic richness of the microbiome is active in regulating metabolism and the metabolic pathogenesis seen in obesity and NAFLD.*[7,9]

However, the application of this obesity model to the human gut is not so straightforward. One study examined the microbial composition of faecal matter from obese patients to approximate the contents of their gut microbiome. It was demonstrated that bacterial ratios in human microbiota were different to that of mouse models; disparities were reported with regard to the representation of Firmicute and Bacteroidetes following ribosomal RNA (rRNA)-based analysis. These findings demonstrate that the biotic changes seen in mice are not always a true reflection of the human microbiome.[9]

Further research has acknowledged that the distribution of gram-negative and gram-positive bacteria may be dependent on body mass index (BMI), with models with a higher BMI showing gut microbial colonisation predominated by gram-negative species.[10,11] An overgrowth of gram-negative species within the gut microbiota has been shown to increase the formation of hepatotoxic substances, such as lipopolysaccharides (LPS), and eventually lead to the deposition of metabolised triglycerides and other SCFA derivatives within the liver, and disturbed lipogenesis.[12,13]

Inflamm tory changes and NAFLD

LPS are considered to hold pro-inflammatory properties when over-produced by the gram-negative bacteria that dominate obesity-associated microbiomes.[14,15] The recognition of LPS by Toll-like receptor 4 (TLR-4), most commonly found in liver cells and resident Kupffer cells, has been shown to be accelerated by mediator inflammatory cytokines, such as tumour necrosis factor α (TNF-α).[16,17] Subsequently, upregulation of the LPS/TLR4 cascade may be influential in the development of progressive inflammation, which is established as a hallmark of NAFLD.[16]

Moreover, the involvement of nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes, sensor molecules involved in recognising bacterial pathogen-associated molecular patterns (PAMPs) within the innate immune system, has been shown to promote insulin resistance.[18,19] Following gut dysbiosis, the liver will receive PAMPs in high concentrations and be considerably vulnerable to their accumulation.[19] NLRP3 is said to activate the cleavage of pro-inflammatory cytokines, pro-IL-1β and pro-IL-18, during the inflammatory drive associated with NAFLD.[19] Pro-inflammatory cytokines, such as the aforementioned, have been recognised as signalling molecules within the insulin signalling pathways of hepatocytes.[20] Thus, the inappropriate cleavage of such proteins may be a potential driver in deranged insulin signalling within the liver and increased insulin resistance.[19,20]

Improving treatment: the involvement of probiotics

Probiotics are live microorganisms administered to confer a beneficial, mutualistic relationship with the host. Prebiotics are fermented products given to induce beneficial changes in the host's gut microbiota and aid healthy gut metabolism. For many years, probiotic and prebiotic treatment has been recognised as a successful therapy in the management of diarrhoeal illness due to their anti-inflammatory properties within the gastrointestinal system.[21] These products are thought to act by reforming an already poorly functioning microbiota and, thus, their role is larger in treating active disease than it is in preventing gut dysfunction.[20,21]

Faecal samples, although not direct quantitative measures of the intestinal microflora, are thought to be accurate surrogate measures of the intestinal content.[21] A study of human faecal samples following treatment suggested that probiotics act as effective competitors against unfavourable bacteria within the gut.[21] The introduction of live gram-positive bacteria via probiotics, in particular Bifidobacteria and Lactobacillus, results in these bacteria dominating the gut microbiome, preventing the over-growth of damaging gram-negative species by way of competition for space and nutrients. In doing so, they reduce the inflammatory consequences of endotoxaemia and prevent stimulation of lipogenesis within the liver.[22]

A meta-analysis of the effects of probiotics upon liver health has also been largely positive, highlighting that probiotics also improve the histological picture of epithelial junctions and liver parenchyma by

reducing gut-epithelial permeability, and reducing the translocation of hepatotoxic products, such as LPS and PAMPS, to the portal circulation.[23,24]

Prebiotics are not themselves digestible by the human host but are intended to support the metabolism of beneficial gut microbiota, allowing them to outgrow unwanted and potentially harmful bacterial microbes.

> *The fibrous content of prebiotics has been shown to minimise the effect of pro-inflammatory cytokines, such as TNF-α, and are considered supportive for those patients who have struggled to maintain a 'gut-friendly' diet.*[25]

For those who have had a consistently large intake of cholesterol and high calorie food over many years, the addition of prebiotics alongside weight loss and dietary changes is thought to have the potential to expedite positive changes to their microbiome.[25]

Furthermore, the use of prebiotics as a form of co-therapy has been suggested as vital in influencing the efficacy of probiotic treatment.[26] Prebiotics, such as fructo-oligosaccharides, can be fermented by both Bifidobacteria and Lactobacillus, aiding their growth and metabolic activity and demonstrating success in reducing hepatic inflammation and improving glucose tolerance.[22,26]

Currently, diet and lifestyle modifications are elemental in the treatment regime of NAFLD, with adequate exercise and restrictions on the consumption of fructose, carbohydrates and saturated fats being advised to patients with weight-related, metabolic conditions.[20] However, the application of probiotics and prebiotics are becoming increasingly more popular in combating hepatic steatosis. The use of these co-therapies is considered favourable to both patients and clinicians due to their availability, accessibility by addition to the diet in food and liquid form, and safety in pregnancy.[27]

Strengths, limitations, and recommendations for future research

It is worth noting that many of the research studies discussed in this paper are mouse models or molecular studies. Whilst these provide a promising, sensible explanation of the role of the gut-liver axis in NAFLD, further research is needed to allow the application of these theories to the human microbiome. Although some high-quality studies and meta-analyses clearly demonstrate the ability of probiotics and prebiotics to reduce hepatic inflammation and improve insulin resistance in humans on a molecular level, the implications of this treatment in improving patient prognosis and recovery is yet to be elucidated.[2,21,22] The use of these treatments in the clinical setting for some gastrointestinal diseases suggests that their therapeutic ability within the human body, and potentially specifically in the liver, should not go overlooked. However, in order to accelerate the incorporation of prebiotic and probiotic treatment into the established management for NAFLD, long-term cohort studies and clinical trials evaluating their efficacy and cost-effectiveness are necessary.

To conclude

The role of gut dysbiosis in amplifying fat accumulation in the liver and development of NAFLD is highly likely to be linked to the imbalance of bacterial colonies within the gut flora and the production of pro-inflammatory metabolites. Research is currently in its infancy, with much of the evidence coming from the use of mouse studies; the mouse microbiome may or may not be comparable to the human microbiome. However, the use of probiotic and prebiotic treatment to actively manage the composition of gut microflora is a promising, novel avenue for treatment that clinicians should be aware of.

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.

References

1. Paquissi FC. Immune Imbalances in Non-Alcoholic Fatty Liver Disease: From General Biomarkers and Neutrophils to Interleukin-17 Axis Activation and New Therapeutic Targets. Frontiers in immunology; 2016, 7: 490.
2. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology; 2016, 64(1):73-84.
3. Alejandra AB, Misael U, Norberto CT, et al. The role of the gut microbiota in the pathology and prevention of liver disease. The Journal of Nutritional Biochemistry; 2018, 60: 1-8.
4. Makoto U, Makoto M, Hayato Y. Gut microbiota and host metabolism in liver cirrhosis. World Journal Of Gastroenterology; 2015, 21(41): 11597–11608.
5. Herbert T, Patrice DC, Emeran AM. Gut microbiome and liver diseases. BMJ Gut: 2016, 65(12): 2035–2044.
6. Klop K, Elte JW, Cabezas MC. Dyslipidemia in Obesity: Mechanisms and Potential Targets. Nutrients; 2013, 5(4): 1218–1240.
7. Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. Nature; 2013, 500: 541-546.
8. Turnbaugh PJ, Bäckhed F, Fulton L, et al. Diet-Induced Obesity Is Linked to Marked but Reversible Alterations in the Mouse Distal Gut Microbiome. Cell host microbe; 2008, 3(4): 213-223.
9. Furet JP, Kong LC, Tap J, et al. Differential adaptation of Human Gut Microbiota to bariatric surgery-induced weight loss. Diabetes; 2012, 59(12): 3049-3057.
10. Duncan SH, Lobley GE, Holtrop G, et al. Human colonic microbiota associated with diet, obesity and weight loss. International journal of obesity; 2008, 32: 1720-1724.
11. Mokhtari Z, Gibson LD, Hekmatdoost A. Non-alcoholic fatty liver disease, the gut, microbiome and diet. Advanced nutrition; 2017, 8(2): 240-252.
12. Kirpich AI, Parajulia D, McClain CJ. The gut microbiome in NAFLD and ALD. Clinical liver disease; 2015, 6(3): 55-58.
13. Adams DH, Eksteen B, Curbishley SM. Immunology of the gut and liver: a love/hate relationship. BMJ Gut; 2008, 57(6): 838-848.
14. Bowen DG., McCaughan GW, Bertolino P. Intrahepatic immunity: a tale of two sites? Cell Press; 2005, 26(10): 512-517.
15. Saltzman ET, Palacios T, Thomsen M, et al. Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Frontiers in Microbiology; 2018, 9: 61.
16. Soares JB, Pimentel-Nunes P, Roncon-Albuquerque R, et al. The role of lipopolysaccharide/toll-like receptor 4 signalling in chronic liver diseases. Hepatology International; 2010, 4(4): 659-672.
17. Rivera CA, Adegboyega P, Rooijen N, et al. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. Journal of Hepatology; 2007, 47: 571–579.
18. Cani P, Amar J, Iglesias MA, et al. Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. Diabetes; 2007, 56(7): 1761-1772.
19. Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature; 2012, 482: 179-185.
20. Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. BMI Gut; 2007, 56(12): 1760–1769.
21. Gratz SW, Mykkanen H, El-Nezami HS. Probiotics and gut health: a special focus on liver diseases. World J Gastroenterol; 2010, 16(4): 403-410.
22. Wong VW, Won GL, Chim AM, et al. Treatment of non-alcoholic steatohepatitis with probiotics. A proof-of-concept study. Annals of Hepatology; 2013, 12 :256–262
23. Ma YY, Yu CH, Shen Z, et al. Effects of probiotics on non-alcoholic fatty liver disease: A meta-analysis. World Journal of Gastroenterology; 2013, 19(40): 6911–6918.

References

24. Lata J, Jurankoya J, Kopacova M, et al. Probiotics in hepatology. World Journal of Gastroenterology; 2011, 17(24): 2890–2896.
25. Vieira AT, Teixeira MM., Martins FS. The role of probiotics and prebiotics in inducing gut immunity. Front. Immunol; 2013, 4: 445.
26. Cani PD, Neyrinck AM, Fava F, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia; 2007, 50(11): 2374–2383.
27. Dugoua JJ, Machado M, Zhu X, et al. Probiotic safety in pregnancy: a systematic review and meta-analysis of randomized controlled trials of Lactobacillus, Bifidobacterium, and Saccharomyces spp. J Obstet Gynaecol Can; 2009, 31: 542–552.

Review

How does oxidative stress during diabetic pregnancy lead to cardiac ventricular septal defects?

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Abstract

Over 60 million women have diabetes worldwide, of which 1.9 million are in the United Kingdom. Pregestational diabetes mellitus (PGDM) related births are around 2% and have tripled in the last 15 years. PGDM can have a disastrous impact on the developing foetus, leading to a variety of birth defects including heart defects. The level of hyperglycaemia determines their prevalence and severity, with oxidative stress mediating the effects. This article seeks to understand how oxidative stress in PGDM can affect the development of the heart, causing ventricular septal defects. References were found using PubMed, with the following terms: "pregestational diabetes", "congenital malformations", "birth defects", "ventricular septal defects" and "oxidative stress". Only articles published in English and after 2007 to the present day were used. Oxidative stress (OS), caused by hyperglycaemia, has been shown to activate the ASK1/JNK1/2 pathway, which affects the development of the heart. It induces apoptosis in the migrating cardiac neural crest cells and decreases cell proliferation in the cardiac outflow tract cushions by targeting several important cyclins and cell cycle inhibitors. Both of these processes lead to the formation of ventricular septal defects due to decreased cellularisation of the cardiac jelly, a precursor of the outflow tract cushions. These findings highlight the importance of glycaemic control during pregnancy as these defects can be prevented by providing mothers with the correct care before and during pregnancy. However, future research is needed to identify potential therapeutic targets of the OS mediated pathways.

Abbreviations

ASK1 - Apoptosis regulating kinase 1
BMP4 - Bone morphogenic protein 4
CNCC - Cardiac neural crest cells
FoxO3a - Forkhead transcription factor 3a
JNK1/2 - c-Jun NH2-terminal kinase 1/2
OFT - Outflow tract
OS - Oxidative stress
PGDM - Pregestational diabetes
ROS - Reactive oxygen species
Trx - Thioredoxin
VSD - Ventricular septal defect

Introduction

Over 60 million women between the ages of 18 and 44 have diabetes worldwide, and around 1.9 million women have diabetes in the United Kingdom.[1,2] This number is all the more worrying when considering the devasting effects diabetes can have on the body and the developing foetus. Pregestational diabetes mellitus (PGDM) can be defined as when a women has type I or type II diabetes before conception.[3]

> *The prevalence of PGDM related births is around 2%, a figure that has almost tripled in the past 15 years.*[4]

Several studies agree that it is not the type of diabetes that mediates the degree of congenital defects but rather the degree of glycaemic control.[2,5] Indeed, a study found that hyperglycaemia in the 1st trimester due to poorly controlled PGDM resulted in major congenital defects in 5-10% of pregnancies and spontaneous abortions in 15-20% of pregnancies.[6] Population studies have shown that PGDM can increase the risk of various birth defects by up to five times, with congenital heart defects being the most frequent malformation due to PGDM, with a relative risk of 3.59 compared to the control population.[4,7] Many congenital heart defects have been linked with PGDM, some of the most prevalent being ventricular septal defects (VSDs) the risk of which are increased by twofold with PGDM.[2,4]

Oxidative stress (OS) has been found to be one of the most likely causes of diabetes related congenital heart disease, however, its mediating pathways are complex.[2] This article presents how OS leads to increased apoptosis and decreased cell proliferation and how this affects the development of the heart, ultimately leading to VSDs.

Methods

Relevant articles were found using the PubMed database (www.ncbi.nlm.nih.gov/pubmed). The following search terms were used in various combinations: "pregestational diabetes", "congenital malformations", "birth defects", "ventricular septal defects" and "oxidative stress". These keywords were considered most relevant to the scope of the article and enabled the identification of relevant papers for this review.

Only papers published in English and after 2007 to the present day were used, as these were deemed most up to date in current research. Once relevant papers were found, their abstracts were read and, if deemed suitable, the whole paper was analysed. Further papers were found by scanning the references of the original papers.

The embryological development of the heart

The heart is formed from the mesoderm 18 days after fertilisation, making it the first functional organ to be developed.[8] Heart development takes place in the cardiogenic area, where the primitive heart tube is formed. The primitive heart tube is made up of five distinct parts: the aortic sac, the outflow tract (OFT), the common primitive ventricle, the atrium and the sinus venosus.[9]

The OFT cushions are formed through a process of cellurisation of the cardiac jelly, an abundant extracellular matrix.[10,11] Cardiac neural crest cells (CNCC) from the dorsal neural tube migrate to the distal region of the OFT whereas, in the proximal region of the OFT, endothelial cells become mesenchymal cells in a process called epithelial to mesenchymal transition.[12] Both regions contribute cells to the cardiac jelly enabling the formation of the OFT cushions, a process that occurs under the influence of bone morphogenic protein 4 (BMP4). BMP4 is necessary for normal embryonic development, acting as a key protein for organogenesis, including CNCC migration as well as OFT septation and formation of membranous portion of ventricular septum.[13] During cardiac remodelling, the OFT cushions grow towards each other and fuse to form a continuous septum and then divide to form the semilunar valves.[11]

How does oxidative stress in women with PGDM affect embryonic development of the heart?

One of the most harmful effects of PGDM is that it induces OS, which has been shown to be responsible for congenital heart defects.[2,13] This is due to the fact that the concentration of reactive oxygen species (ROS) increases in conjunction with increasing glucose levels in PGDM.

> *ROS have been found to reduce the cells' antioxidant capacities, which leaves them vulnerable to increased apoptosis and decreased cell proliferation.*[6]

A study performed on chicks found that the OFT cushions were asymmetrical causing the lumen of the heart to be displaced in six out of the ten diabetic chicks compared to zero out of the ten control chicks.[5] This was hypothesised to be due to decreased cell proliferation in the OFT cushions as a result of decreased levels of cyclin D1 and increased levels of p21. Cyclins, such as cyclin D1, enable cell progression from the G1 phase to S phase, whereas cell cycle inhibitors, such as p21, cause cell cycle arrest at G1, therefore inhibiting DNA replication and mitosis.[14] Hyperglycaemia in PGDM has been found to decrease gene expression of cyclin D1 by threefold and increase gene expression of p21 by twofold, leading to decreased cell proliferation due to cell cycle arrest.[14]

A 2014 study evaluated the cellularisation of the cardiac jelly necessary for OFT development and found that the control group contained more than double the amount of mesenchymal cells compared to the diabetic group.[10] This was attributed to a decreased rate of cell mitosis in the diabetic group (17.93%) compared to the control group (35.85%). Furthermore, the study found elevated levels of OS localised to the OFT cushions.

A 2008 study that found that OS induced on E7.5 lead to a range of OFT defects in diabetic mice, despite the fact that OFT development occurs after E7.5.[15] They attributed the defects to apoptosis of CNCC, as apoptotic cells were found along the path of CNCC migration. This finding was also echoed by Zhao *et al.* (2012) who found decreased CNCC migration as a result of OS.[16]

Another study conducted in mice found that during embryonic day 10.5 of development (E10.5) diabetic mice were more susceptible to OFT stenosis resulting in smaller OFT cushions and a thinner right ventricle.[17] They also detected VSD at E15.5 due to suppressed development of OFT cushions at earlier stages of the embryonic development. They found decreased cell proliferation markers in the OFT cushions, but very few apoptotic cells were detected. This would indicate that decreased cell proliferation, as opposed to increased apoptosis was responsible for these VSDs.

A 2011 study made an interesting finding that hyperglycaemia affected OFT cushion development at E8.5 as opposed to OFT cushion remodelling at E11.5 as rates of VSDs were higher in mice made hyperglycaemic from E8.5 (49.2%) as opposed to mice made hyperglycaemic from E11.5 (6.2%).[16]

These studies all indicate that PGDM induces increased apoptosis in CNCC migration and decreases cell proliferation in OFT cushions, mediated by oxidative stress.

The role of ASK1 pathways in oxidative stress mediated VSDs

Despite oxidative stress being a commonly acknowledged cause of congenital heart defects, the pathways by which it affects embryonic development have been disputed. Earlier studies reported that oxidative stress inhibited the expression of the *pax3* gene, causing apoptosis through the expression of p53 (a tumour suppressor gene), which is normally suppressed by *pax3*.[15] However, recent studies have found a more likely pathway.[2,13,18] Apoptosis-signal-regulating kinase 1 (ASK1) was discovered as key in mediating the effects of OS on foetal cells (see **Figure 1**).[2]

ASK1 is part of the mitogen-activated protein kinase cascade, normally forming an inactivate complex with thioredoxin (Trx), which

plays a key role in cell growth, cell cycle regulation, and apoptosis.[13,19] A study measured the levels of ASK1/Trx complex, as well as the levels of oxidised Trx, and found lower levels of ASK1/Trx complex but much higher levels of oxidised Trx in hearts of diabetic mice compared to control mice.[13] This is due to oxidisation of Trx through ROS, hence dissociating Trx form the Ask1/Trx complex, enabling ASK1 activation.[13,18]

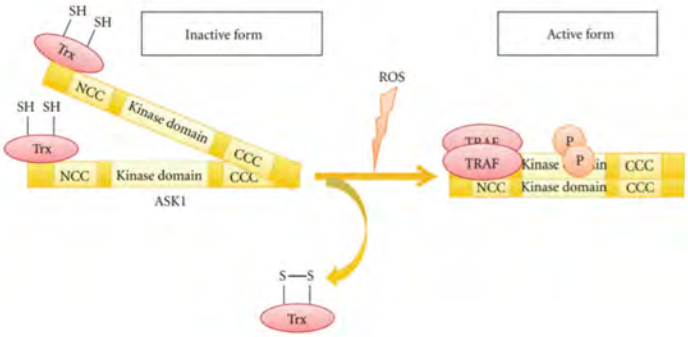

Figure 1. The role of ASK1 in OS. Trx retains ASK1 in its inactive form. However, ROS causes dissociation of Trx from ASK1, leading to activation of ASK1 by tumour necrosis factor receptor-associated factor (TRAF). CCC, C-terminal coiled-coil domain; NCC, N-terminal coiled-coil domain; P, phosphate. Figure adapted from Soga *et al*,[22] distributed under a CC BY 3.0 license, which permits unrestricted use, distribution, and reproduction in any medium.

Indeed, high levels of ASK1 were detected in embryonic hearts of diabetic mice at E12.5, a key stage of cardiogenesis. To prove that ASK1 mediates the teratogenic effects of OS on the embryo, the study examined the effects of ASK1 deletion on the prevalence of maternal diabetes induced congenital heart defects. The authors found that under diabetic conditions, one out of the 54 ASK1 negative diabetic mice showed congenital heart defects compared to 14 out of 55 control diabetic mice.[13]

ASK1 induces its effects through activation of the c-Jun NH2-terminal kinase 1/2 (JNK 1/2).[2,13,18] JNK1/2 has been shown to increase the activity of the Forkhead transcription factor 3a (FoxO3a) which up-regulates TNFR1 associated death domain (TRADD), triggering caspase 8 activation, causing apoptosis.[2,13] ASK1 deletion inactivates the JNK1/2 pathway by suppressing its phosphorylation.[13] This, in turn, was shown to abrogate the activation of FoxO3a as fewer apoptotic cells were detected in ASK1 negative diabetic mouse hearts compared to control diabetic mouse hearts.

However, apoptosis is not the only mechanism by which ASK1 disrupts normal embryonic development of the heart. It has previously been shown that decreased cell proliferation plays a critical role in OFT defects. ASK1 was found to mediate this effect as ASK1 deletion abrogated both decreases in cyclin D1 and increases in p21.[13] This, therefore, indicates that the ASK1-JNK1/2 pathway mediates the effects of oxidative stress on cell proliferation.

Furthermore, BMP4 plays a critical role in cardiac development.[13,20] The downregulation of BMP4 leads to decreased mitosis in OFT cushions, with a study showing deletion of BMP4 resulted in VSD in the membranous portion of the ventricular septum in 17 out of 19 BMP4 negative mice.[21] PGDM was found to significantly decrease levels of BMP4 in diabetic mice, but the effects of PGDM on BMP4 expression were diminished in ASK1 negative diabetic mice.[13]

It is, however, relevant to note that despite these findings being important, these studies are limited due to them being conducted in animals such as mice or chicks. Despite these acting as a useful comparison to human biology, they are not interchangeable, and therefore findings must be considered with this limitation in mind.

Conclusion

PGDM has damaging effects on the development of the foetal heart, in particular the OFT. Research has shown an important link between hyperglycaemia and OS, with there being a positive correlation between levels of ROS and glucose levels in PGDM. ROS leave cells vulnerable to increased apoptosis during cardiac neural crest cell migration to the cardiac jelly. ROS also causes decreased cell proliferation in the development of the OFT cushions.

These teratogenic effects are mediated through the ASK1-JNK1/2 pathway. This affects cyclins and cell cycle inhibitors leading to a decrease in cell proliferation and mitosis in embryonic hearts affected by PGDM. It also has an inhibitory effect on BMP4, leading to an increased risk of VSDs in the membranous portion of the ventricular septum. Finally, it initiates apoptosis through the FoxO3a-TRADD pathway. All of these culminate in reducing cell density in OFT cushions, leading to a variety of congenital heart diseases including VSDs.

These devasting congenital heart diseases are preventable through better glycaemic control during pregnancy, which can be achieved by ensuring that everyone receives the correct care before and during pregnancy. This key topic would benefit from additional research, exploring how the OS pathway could be used as a therapeutic target to prevent VSDs.

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

References

1. Diabetes UK (2014). Facts and stats. Available from: https://mrc.ukri.org/documents/pdf/diabetes-uk-facts-and-stats-june-2015/. Accessed: 23 November 2020
2. Gabbay-Benziv R, Reece EA, Wang F,et al. Birth defects in pregestational diabetes: Defect range, glycemic threshold and pathogenesis. World J Diabetes. 2015;6(3):481–8.
3. Fong A, Serra A, Herrero T, et al. Pre-gestational versus gestational diabetes: a population based study on clinical and demographic differences. J Diabetes Complications. 2014;28(1):29–34.
4. Agha MM, Glazier RH, Moineddin R, et al. Congenital abnormalities in newborns of women with pregestational diabetes: A time-trend analysis, 1994 to 2009. Birth Defects Res Part A Clin Mol Teratol. 2016;106(10):831–9.
5. Lawson TB, Scott-Drechsel DE, Chivukula VK, et al. Hyperglycemia Alters the Structure and Hemodynamics of the Developing Embryonic Heart. J Cardiovasc Dev Dis. 2018;12;5(1):13.
6. Ornoy A, Reece EA, Pavlinkova G, et al. Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes. Birth Defects Res Part C Embryo Today Rev. 2015;105(1):53–72.
7. Hoang TT, Marengo LK, Mitchell LE, et al. Original Findings and Updated Meta-Analysis for the Association Between Maternal Diabetes and Risk for Congenital Heart Disease Phenotypes. Am J Epidemiol. 2017;186(1):118–28.
8. Betts G, Desaix P, Johnson E, et al (2021). Development of the heart BC campus. Available from: https://opentextbc.ca/anatomyandphysiology/chapter/19-5-development-of-the-heart/ Accessed: 16 February 2021
9. Lumen Learning (2021). Development of the heart Lumen Learning. Available from: https://courses.lumenlearning.com/suny-ap2/chapter/development-of-the-heart/. Accessed: 16 February 2021

10. Zhao Z. TGFβ and Wnt in cardiac outflow tract defects in offspring of diabetic pregnancies. Birth Defects Res B Dev Reprod Toxicol. 2014;101(5):364–70.
11. Lin C-J, Lin C-Y, Chen C-H, et al. Partitioning the heart: mechanisms of cardiac septation and valve development. Development. 2012;139(18):3277–99.
12. Cardiology E society of (2009). An introduction to outflow tract defects. Available from: https://www.escardio.org/Working-groups/Working-Group-on-Development,-Anatomy-and-Pathology/Publications/An-introduction-to-outflow-tract-development. Accessed: 16 February 2021
13. Wang F, Wu Y, Quon MJ, et al. ASK1 mediates the teratogenicity of diabetes in the developing heart by inducing ER stress and inhibiting critical factors essential for cardiac development. Am J Physiol Endocrinol Metab. 2015;309(5):E487–99.
14. Scott-Drechsel DE, Rugonyi S, Marks DL, et al. Hyperglycemia slows embryonic growth and suppresses cell cycle via cyclin D1 and p21. Diabetes. 2013;62(1):234–42.
15. Morgan SC, Relaix F, Sandell LL, et al. Oxidative stress during diabetic pregnancy disrupts cardiac neural crest migration and causes outflow tract defects. Birth Defects Res A Clin Mol Teratol. 2008;82(6):453–63.
16. Zhao Z. Endoplasmic Reticulum Stress in Maternal Diabetes-Induced Cardiac Malformations During Critical Cardiogenesis Period. Birth Defects Res Part B Dev Reprod Toxicol. 2012;95(1):1–6.
17. Zhao Z. Cardiac malformations and alteration of TGFβ signaling system in diabetic embryopathy. Birth Defects Res Part B Dev Reprod Toxicol. 2010;89(2):97–105.
18. Li X, Weng H, Xu C, et al. Oxidative stress-induced JNK1/2 activation triggers proapoptotic signaling and apoptosis that leads to diabetic embryopathy. Diabetes. 2012;61(8):2084–92.
19. Sayama K, Hanakawa Y, Shirakata Y, et al. Apoptosis Signal-regulating Kinase 1 (ASK1) Is an Intracellular Inducer of Keratinocyte Differentiation. J Biol Chem. 2001;276(2):999–1004.
20. Kumar SD, Dheen ST, Tay SSW. Maternal diabetes induces congenital heart defects in mice by altering the expression of genes involved in cardiovascular development. Cardiovasc Diabetol. 2007;6:34.
21. McCulley DJ, Kang J-O, Martin JF, et al. BMP4 is required in the anterior heart field and its derivatives for endocardial cushion remodeling, outflow tract septation, and semilunar valve development. Dev Dyn. 2008;237(11):3200–9.
22. Soga M, Matsuzawa A, Ichijo H. Oxidative Stress-Induced Diseases via the ASK1 Signaling Pathway. International Journal of Cell Biology. 2012; 2012:439587.

Review

Insights for cardiology from chaos theory

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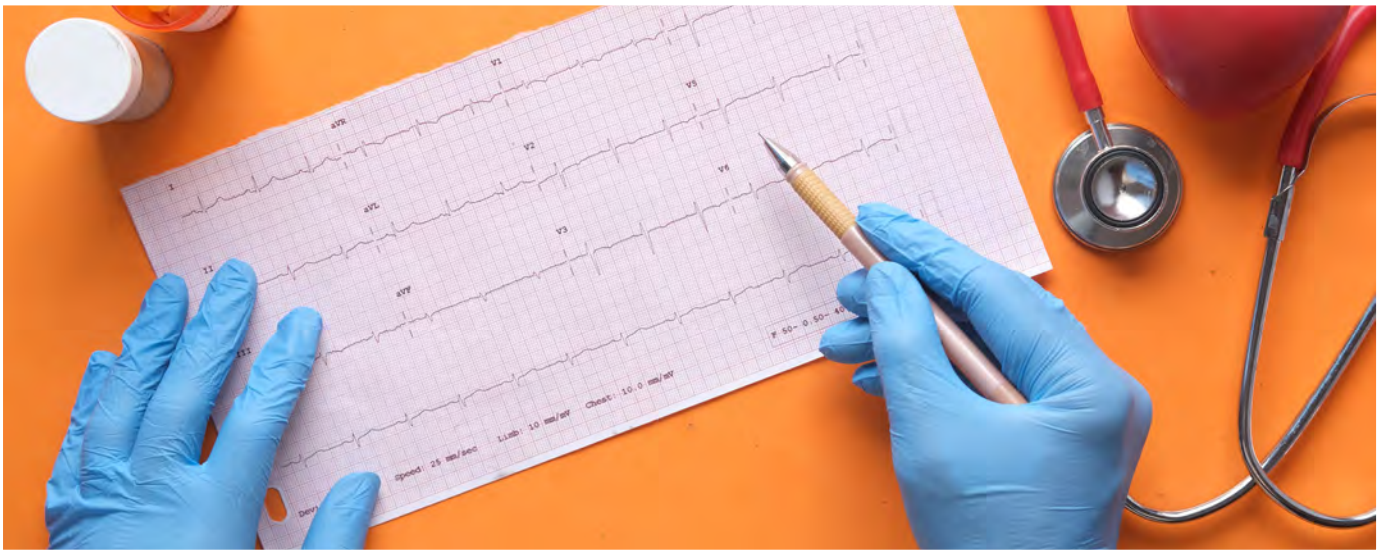

Abstract

Non-linear mathematical models uncover features of physiological systems that are missed by linear approaches. Chaos, a type of non-linear motion, is an inherent feature of health. Its study provides insights into several fields, including neurology, epidemiology, and cardiology. However, chaos is largely unknown in health science and when it is known, it is not actively investigated due to its mathematical complexity and computational demands. This review introduces chaos theory to health researchers without a formal background in the physical sciences to address the interdisciplinary learning barrier. Comparisons between chaos theory and classical linear systems are drawn to provide an accessible, qualitative introduction to chaos before exploring its genesis and consequences in the cardiovascular system. Breakup of spiral wave action potentials (SWAPs) is shown to be identical to mechano-electrical feedback (MEF) as a route to cardiological chaos. SWAP breakup contributes to arrhythmogenesis alongside tissue heterogeneities and the complex perfusion geometry resulting from ischaemia. Together with the recent success of novel chaotic metrics for obstructive sleep apnoea (OSA) and haemodynamics, a widespread adoption of non-linear systems theory in the health sciences is encouraged to complement existing linear methods.

Abbreviations

AP - Action potential
BR - Border region
CD - Correlation dimension
DFA - Detrended fluctuation analysis
EC - Ephaptic coupling
ECG - Electrocardiogram
FD - Fractal dimension
gPC - Generalised polynomial chaos expansion
HRV - Heart rate variability
MEF - Mechano-electrical feedback
MLE - Maximal Lyapunov exponent
OSA - Obstructive sleep apnoea
PS - Phase synchronisation
SCD - Sudden cardiac death
SR - Sarcoplasmic reticulum
SWAP - Spiral wave action potential

Introduction

Chaos theory may provide ground-breaking solutions to previously unsolved problems in physiology. Originating from the physical sciences, this non-linear model offers insight through its ability to uncover emergent phenomenology and hidden dynamics that are missed by linear methods.[1] Current health science literature employs linear models almost universally while non-linear methods remain largely unknown. Despite this, chaos theory has diverse biomedical applications, including in epidemiology, neurology, and healthcare organisation.[2]

In the cardiovascular system, chaotic analysis may be used to investigate cardiac instabilities, such as alternans, arrhythmia and heart rate variability (HRV), cardiomyocyte coupling, and unique metrics for diagnosis.[1,3,4] However, chaotic networks are mathematically complex, containing numerous intricate interactions between system elements. Efficient simulations of large chaotic networks are therefore difficult to study without significant computational power.[5] Mathematical approximations are often used to overcome this issue, at the expense of simulation accuracy. Despite these shortcomings, perhaps the greatest limitation of chaos theory is the interdisciplinary learning barrier it poses to health scientists.

The aims of this review are to introduce the topic of chaos qualitatively, to explore cardiology from a non-linear perspective using recent literature, to demonstrate the usefulness of chaotic analysis and to propose new directions for cardiology research.

Methodology

The PubMed and Google Scholar databases were used to source relevant and timely material. Initially, the Boolean search terms "chaos" and "cardiology", "cardiovascular" or "cardiac" (with all variations) were employed and 612 articles were identified. General research into chaos did not constrain articles by publication date. Cardiology research required material to be published between October 2018 and April 2020. Of the remaining 40 articles, 12 were disregarded as they did not investigate or utilise mathematical chaos. Of these, a total of 16 articles were selected to be analysed based on content and scope for comparison; these articles primarily focussed on the alleged role of chaotic dynamics in arrhythmogenesis.

Chaos: an introduction

Physiological systems can demonstrate five levels of mathematical order: equilibrium, periodicity, quasi-periodicity, chaos, and random motion.[6] The first three levels of order are linear, meaning any change to an input variable results in a well-behaved systemic response. Simply, small changes produce small effects while large changes produce large effects. Chaos, however, is neither fully linear nor fully random. Instead, it occupies a niche middle-ground, containing features of both extremes.

> *Chaotic systems appear disorderly yet, like linear systems, their ability to be captured by mathematics makes them fully deterministic; any future state can be calculated from an initial, or indeed any other, state.[2] Chaotic systems are therefore described as non-linear.*

Like all non-linear systems, chaos is extremely sensitive to initial conditions. A vanishingly small change to the initial state of the system produces errors that accumulate over time, resulting in large qualitative changes in dynamics.[6] Any attempt to predict the system trajectory in the future will also attract errors. A calculated final state will therefore contain a high degree of uncertainty. In other words, although chaotic motion may be described deterministically using equations, exponential error growth means it is unpredictable overall. The resulting dynamics evolve erratically and, to the uninitiated, appear fully random. An intuitive example of this behaviour is that of the double pendulum (**Figure 1**). Some key differences between conventional linear systems and their chaotic counterparts are outlined in **Table 1**.

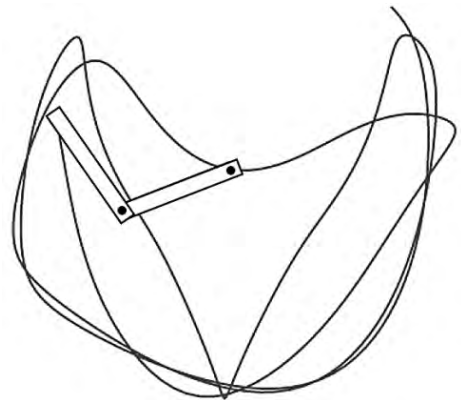

Figure 1. A possible trajectory of the chaotic double pendulum. The position of the system at a future time can be calculated from its initial position (deterministic), but with little certainty (unpredictable) due to errors from initialisation that grow over time. In cardiology, this motion is naturally seen in heart rhythm. This figure was produced using a Python simulation.

Table 1. Key features of linear and chaotic systems.

	Linear systems	Chaotic systems
Equations	Always described by simple equations.	Sometimes described by simple equations. Sometimes described by intricate equations. May be approximated as linear systems (linearisation).
Exponents	All terms are linear; all variables are raised to first power only.	At least one term is curved; at least one variable raised to non-unity power.
Behaviour of solutions	Gradual changes in behaviour; time series are regular. Any solution may be written as the sum of linearly-independent components.	Abrupt changes in behaviour; time series are erratic and have fractal nature. Time series therefore appear similar at different scales (self-similarity).
Determinism	Fully deterministic and predictable.	Fully deterministic. Predictable in the absence of error (pure mathematics). Unpredictable otherwise (simulations, human physiology).
Sensitivity	Uniformly sensitive: changes to the initial state are reflected equally by system dynamics.	Extremely sensitive: changes to the initial state cause large, unexpected changes to dynamics.

Information derived from Rickles et al, 2007[2] and Sharma 2009.[6]

Chaos appears to be a physiological determinant of health while a loss of chaos is associated with a loss of health.[2]

> *Within cardiology, chaos manifests itself in heart rhythm regularity; a mathematically complex heart rhythm is generally healthy.[7] However, if incoherent electrical activity leads to a loss of chaos, complexity can remain despite new-found cardiac pathologies.[8]*

It is this promise of emergent phenomenology that often motivates the study of chaos; can specific parameter values give rise to previously unseen phenomena?

Cardiovascular origins of chaos and irregular cardiac dynamics

Dynamical chaos arises through several mechanisms in cardiac electrophysiology. The breakup of spiral wave action potentials (SWAPs) is particularly relevant due to its alleged role in arrhythmogenesis.[5] SWAPs propagate through cardiac tissue with a

three-dimensional spiral geometry (**Figure 2**) and become unstable when perturbed. This instability leads each SWAP to fragment and reform. The resulting waves compete with activity from the sinoatrial node and are described as re-entrant; they traverse around the same anatomical circuit.[9,10] Consequently, irregular cardiac dynamics and cardiac instabilities arise.

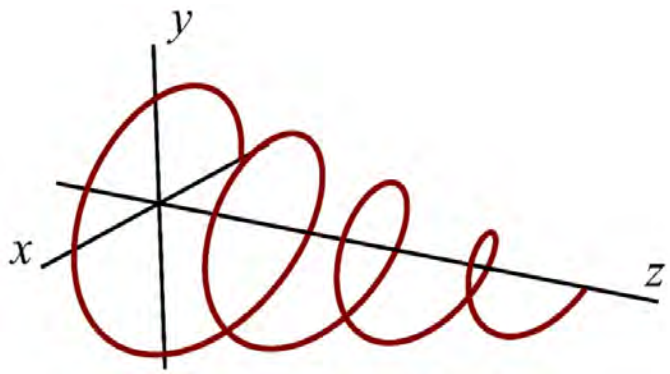

Figure 2. SWAPs occur naturally within the heart and have a corkscrew-like shape. The SWAP tip is the point of intersection between the wave and the *z*-axis. This figure was produced using a Python simulation.

The introduction of time delays to cardiomyocyte Ca^{2+} channels has recently been found to cause SWAP breakup.[5] Alternations in the amplitude (amplitude alternans) or time intervals (temporal alternans) between successive electrocardiogram (ECG) peaks arise from this approach[11] and are associated with arrhythmia and sudden cardiac death (SCD).[3]

A new approach using delay differential equations appears promising.[5] It drastically simplifies highly non-linear SWAP systems whilst maintaining important qualitative features of the dynamics. The model is therefore simple and well-optimised, making the study of SWAPs accessible to health scientists who lack powerful computer hardware or a mathematical background. Additionally, two independent treatments of SWAP propagation may provide novel approaches to instability research; a non-localised model[9] and a statistical model.[12]

Re-entrant wave breakup is however not the only route to chaos. Mechano-electrical feedback (MEF) occurs when tissue deformation affects action potential (AP) propagation. One study reports that MEF induced by pacing cardiac cells at sufficiently high rate resulted in an alternating AP duration.[3] This is consistent with the temporal alternans that pre-empt ventricular fibrillation and SCD.[13] The rate of AP repolarisation initially accelerated before slowing, prolonging the pre-peak time and decreasing the post-peak time.[3] This result may be reinterpreted; we can conceive that each AP instead experienced an effective time delay due to the change in polarisation speed.

> *The authors' results are therefore consistent with the delay differential equation approach,[5] showing MEF and delay-induced SWAP breakup have an identical effect on electrophysiology and instability development.*

Fluctuations in sarcoplasmic reticulum (SR) load have been shown to cause amplitude alternans.[14] The mechanism involves non-linear interactions between Ca^{2+} release and local voltage. Continuous phase transition to alternans occurs at a high rate of SR Ca^{2+} re-entry. By comparing with other studies,[3,5,13] it appears that alternans develop when charge movement in cardiac tissue surpasses a threshold frequency, though this insight requires confirmation by future research.

Cardiac dynamics are also affected by external sources.

> *Cardio-respiratory coupling during respiratory sinus arrhythmia has been quantified using a new model of chaotic phase synchronisation (PS): a measure of the degree to which two or more time series may be superimposed.[15]*

Both the simulated and experimental respiratory signals utilised in one study[7] had an insignificant effect on cardiac dynamics, a result that supports the hypothesis that the vascular system has a greater effect on cardiac dynamics than the respiratory system.[15] Some of the authors' assumptions should be questioned however.[7] White and red noise were used to randomise respiration and heart rate, respectively. The use of two different noise colours is never justified by the authors and others report that white noise is not applicable to heart rate.[9] Unequal inhalation and exhalation durations are also acknowledged in some studies,[15] but not in others.[7] Cardio-respiratory interplay should therefore be investigated further.

Separately, the study reports that chaos can originate from the autonomic control of local vasculature.[7] Two chaotic metrics were utilised: fractal dimension (FD), which tracks changes in dynamical complexity, and the maximal Lyapunov exponent (MLE), which evaluates system predictability. This result is well agreed upon.[15,16]

Pathological chaos and diagnostic metrics

In addition to SWAP breakup and alternans,[3,5] electrophysiological gradients cause arrhythmia[4] by interrupting AP propagation. Conduction is affected by the shape of the border region (BR) between perfused and non-perfused tissue in ischaemia and by a recently discovered conduction mechanism involving extracellular ion movement, known as ephaptic coupling (EC).[17] High BR complexity and strong EC were found to promote conduction in the ischaemic region, reducing the likelihood of arrhythmia.

The trajectory of SWAP tips is another determinant of arrhythmia. In homogeneous media, tip dynamics are stable and periodic. Circularly symmetric tissue heterogeneities can however transition SWAP tips to chaos. This result is independent of wave dynamics, and supposedly suggests SWAP breakup is not a prerequisite for arrhythmogenesis.[8] However, the authors also note that chaotic tip trajectories drive SWAP breakup itself. SWAP tips may therefore only cause arrhythmogenesis indirectly through breakup. Arrhythmia resulting from chaotic tip trajectories therefore require further study, with the inclusion of signal noise to better mimic real cardiac electrophysiology.

A recent article found that patients with obstructive sleep apnoea (OSA) are identified more readily using chaotic analysis of HRV time series than with ECGs.[1] In OSA, heart rate varies periodically between bradycardia and tachycardia. Conventionally, non-linear detrended fluctuation analysis (DFA) is used to analyse ECG data for OSA. Analysis of HRV time series with chaotic correlation dimension (CD), a measure of complexity, had an associated p-value of $p=0.003$, whereas ECG DFA had a p value of $p=0.044$. This result is statistically significant ($p<0.05$). In addition, the authors' conclusion that sympathetic responses increase during apnoea should be investigated further due to the aforementioned link with the development of cardiac instability.[7,16]

Evaluating the reliability of cardiovascular models is essential for clinical applications. Systems may be assessed using the polynomial chaos expansion (gPC). This novel technique provides information about prospective models by calculating the mean, standard

deviation, and other relevant statistics. gPC also measures system sensitivity to changing parameters, a defining feature of chaos, and provides an estimation of errors. Currently, gPC is finding success in several areas of cardiology. In studies of ventricular wall thickness,[18,19] conventional approaches and gPC agree to within 2%. A recent application used gPC to assess the decrease in blood pressure that occurs during arterial stenosis and found a similarly accurate result.[20] The technique was also noted to be far more efficient than traditional methods, completing instantly where other approaches required two weeks.

> *Not only does this overcome the computational barriers that are posed by chaotic simulations, gPC may eventually be used in diagnosis; patient-specific analysis has already been demonstrated in studies of blood flow.[21]*

Conclusion

Chaos theory offers new approaches in physiology. Recent simplifications to SWAP models have made the study of cardiological chaos accessible to health scientists. Functionally identical to MEF, delay-induced SWAP breakup is an important route to chaos as it produces alternans, through Ca^{2+} release and chaotic tip trajectories, that are associated with arrhythmia and SCD. Alternans also arise from the interaction of APs with ischaemic BRs or extracellular Ca^{2+} ions. Origins of irregular cardiac dynamics and instabilities are therefore numerous and varied.

In general, alternans appear to result from the oscillatory movement of charge above a frequency threshold, though this is unconfirmed. The effect of the respiratory system on cardiac dynamics and a causal link between tip dynamics and arrhythmogenesis, independent of SWAP breakup, are yet to be established.

> *The chaotic metrics of phase synchronisation (PS), fractal dimension (FD), maximal Lyapunov exponent (MLE), correlation dimension (CD) and polynomial chaos expansion (gPC) aid new research.*

In diagnosis, CD already improves on conventional methods to identify OSA patients, while gPC overcomes the limitation of simulation efficiency and demonstrates patient-specific use. Future literature is likely to locate similar uses for the other chaotic metrics as non-linear techniques become more widely utilised in health science.

Though broad prerequisite knowledge is often required, non-linear models clearly complement linear approaches and the success of chaos theory in current research justifies its future study.

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References

1. Ataei M, Naghsh S, Yazdchi M, et al. Chaos-based analysis of heart rate variability time series in obstructive sleep apnea subjects. Journal of Medical Signals & Sensors. 2020;10(1):53.
2. Rickles D, Hawe P, Shiell A. A simple guide to chaos and complexity. Journal of Epidemiology & Community Health. 2007;61(11):933-937.
3. Hazim A, Belhamadia Y, Dubljevic S. Effects of mechano-electrical feedback on the onset of alternans: A computational study. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(6):063126.
4. Wei N, Tolkacheva E. Interplay between ephaptic coupling and complex geometry of border zone during acute myocardial ischemia: Effect on arrhythmogeneity. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2020;30(3):033111.
5. Moreira Gomes J, Lobosco M, Weber dos Santos R, et al. Delay differential equation-based models of cardiac tissue: Efficient implementation and effects on spiral-wave dynamics. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(12):123128.
6. Sharma V. Deterministic Chaos and Fractal Complexity in the Dynamics of Cardiovascular Behavior: Perspectives on a New Frontier. The Open Cardiovascular Medicine Journal. 2009;3(1):110-123.
7. Karavaev A, Ishbulatov Y, Ponomarenko V, et al. Autonomic control is a source of dynamical chaos in the cardiovascular system. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(12):121101.
8. Lombardo D, Rappel W. Chaotic tip trajectories of a single spiral wave in the presence of heterogeneities. Physical Review E. 2019;99(6).
9. Gurevich D, Grigoriev R. Robust approach for rotor mapping in cardiac tissue. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(5):053101.
10. Cytrynbaum E, MacKay V, Nahman-Lévesque O, et al. Double-wave reentry in excitable media. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(7):073103.
11. Thompson, R. Using Delay-Differential Equations for Modeling Calcium Cycling in Cardiac Myocytes. Thesis. Rochester Institute of Technology. 2013.
12. Vidmar D, Rappel W. Extinction dynamics of spiral defect chaos. Physical Review E. 2019;99(1).
13. Kesmia M, Boughaba S, Jacquir S. Nonlinear dynamics of two-dimensional cardiac action potential duration mapping model with memory. Journal of Mathematical Biology. 2019;78(5):1529-1552.
14. Romero L, Alvarez-Lacalle E, Shiferaw Y. Stochastic coupled map model of subcellular calcium cycling in cardiac cells. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2019;29(2):023125.
15. Lin C, Lin P, Wang C, et al. Probing age-related changes in cardio-respiratory dynamics by multimodal coupling assessment. Chaos: An Interdisciplinary Journal of Nonlinear Science. 2020;30(3):033118.
16. Moura-Tonello S, Carvalho V, Godoy M, et al. Evaluation of Cardiac Autonomic Modulation Using Symbolic Dynamics After Cardiac Transplantation. Brazilian Journal of Cardiovascular Surgery. 2019;34(5).
17. Lin J, Keener J. Ephaptic Coupling in Cardiac Myocytes. IEEE Transactions on Biomedical Engineering. 2013;60(2):576-582
18. Campos J, Sundnes J, dos Santos R, et al. Effects of left ventricle wall thickness uncertainties on cardiac mechanics. Biomechanics and Modeling in Mechanobiology. 2019;18(5):1415-1427.
19. Rodríguez-Cantano R, Sundnes J, Rognes M. Uncertainty in cardiac myofiber orientation and stiffnesses dominate the variability of left ventricle deformation response. International Journal for Numerical Methods in Biomedical Engineering. 2019;35(5):e3178.
20. Heinen S, Gashi K, van den Heuvel D, et al. A Metamodeling Approach for Instant Severity Assessment and Uncertainty Quantification of Iliac Artery Stenoses. Journal of Biomechanical Engineering. 2019;142(1).
21. Boccadifuoco A, Mariotti A, Capellini K, et al. Validation of Numerical Simulations of Thoracic Aorta Hemodynamics: Comparison with In Vivo Measurements and Stochastic Sensitivity Analysis. Cardiovascular Engineering and Technology. 2018;9(4):688-706.

Review

Silicone breast implants versus deep inferior epigastric perforator flap: a comparative analysis of two approaches to breast reconstruction following mastectomy

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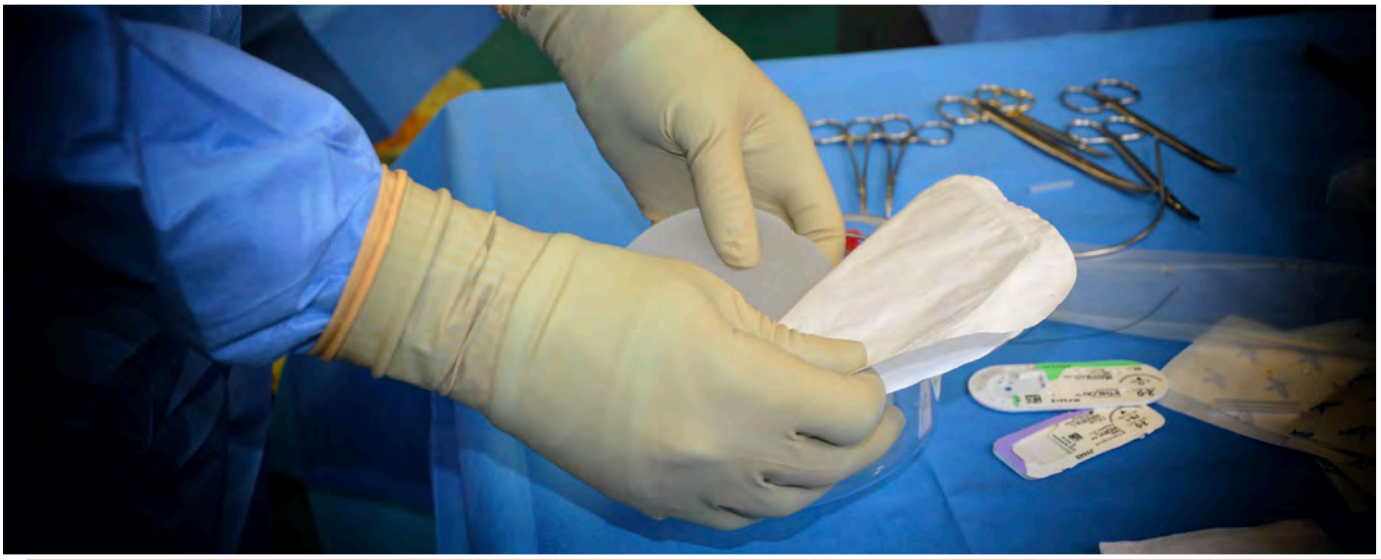

Abstract

Approximately 150 new cases of breast cancer are diagnosed daily in the UK and 81% of breast cancer patients undergo surgery as part of the management of their primary tumour. Consequently, breast reconstruction surgery is becoming increasingly prevalent and is a branch of plastic surgery that is constantly developing. Silicone breast implants and the deep inferior epigastric perforator (DIEP) flap are two forms of breast reconstruction used by the NHS to help recreate the physical appearance of breast tissue. Silicone breast implants provide patients with a more immediate result and related positive mental health outcomes, but are associated with complications and increased health risks in the longer term. These health risks include capsular contracture and breast-implant-associated anaplastic large cell lymphoma (BIA-ALCL), which often require subsequent surgical management. Conversely, the DIEP flap is associated with longer hospital stays and increased post-operative pain in the short-term, but better long-term prospects in terms of reduced incidence of complications and adverse health reactions. As the DIEP flap is an autologous breast reconstruction surgery, using the patients' own tissue, there are no risks of rejection or cancer as seen with silicone breast implants. Whilst DIEP flap reconstruction is initially more expensive than silicone implant reconstruction, the shorter hospital length of stay and reduced incidence of complications requiring surgical revisions diminishes the cost difference. Further research is recommended to analyse the total long-term costs of both approaches to better understand which offers the best outcome for patients and the best value for the NHS.

Abbreviations

ALCL - Anaplastic large cell lymphoma
BIA-ALCL - Breast-implant-associated anaplastic large cell lymphoma
CT - Computerised tomography
DIEP - Deep inferior epigastric perforator
FDA - Food and Drug Administration
MDR - Medical device report
PFD - Pirfenidone
WHO - World Health Organization

Introduction

Following a mastectomy, many women are left feeling unsatisfied with the image of their breasts and breast reconstruction serves as a way for them to restore the physical appearance of their breasts.[1] However, there are different approaches to breast reconstruction, and each varies in procedure and outcome. Breast implants, invented by Cronin in 1961,[2] account for 80% of implant procedures and are a popular choice for breast reconstruction.[3] The implant material referred to in this review is silicone as this is the most common form of breast implant in the UK.[4] An alternative to breast implants is the deep inferior epigastric perforator (DIEP) flap, which removes the skin of the abdominal area, along with the deep inferior epigastric artery and vein, while leaving the rectus abdominis muscle and fascia intact, to reconstruct the breast (**Figure 1**).[5] This literature review compares silicone breast implants with DIEP flap surgery in the reconstruction

of the breast to evaluate which is more advantageous for patients seeking breast reconstruction following mastectomy.

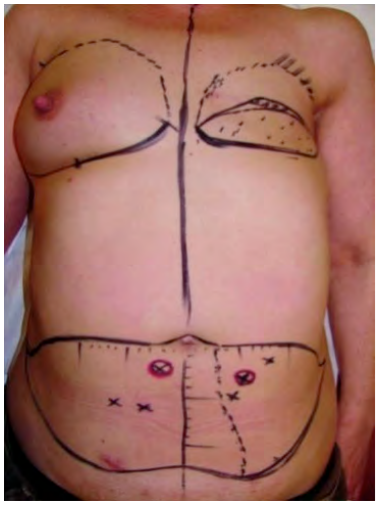

Figure 1. An image illustrating the DIEP flap for breast augmentation of both left and right breast. Perforator arteries of the deep inferior epigastric are indicated by the crosses. Image from Hamdi and Rebecca (2006),[5] copyright holder: www.thieme.com (reprinted by permission).

Methodology

For this report, an initial search of 'breast reconstruction' AND 'silicone breast implants' OR 'DIEP flap' was carried out in medical databases. Inclusion criteria were research articles that reviewed the short- or long-term outcomes of breast augmentation with large population cohorts or specific clinical cases (see **Figure 2**)

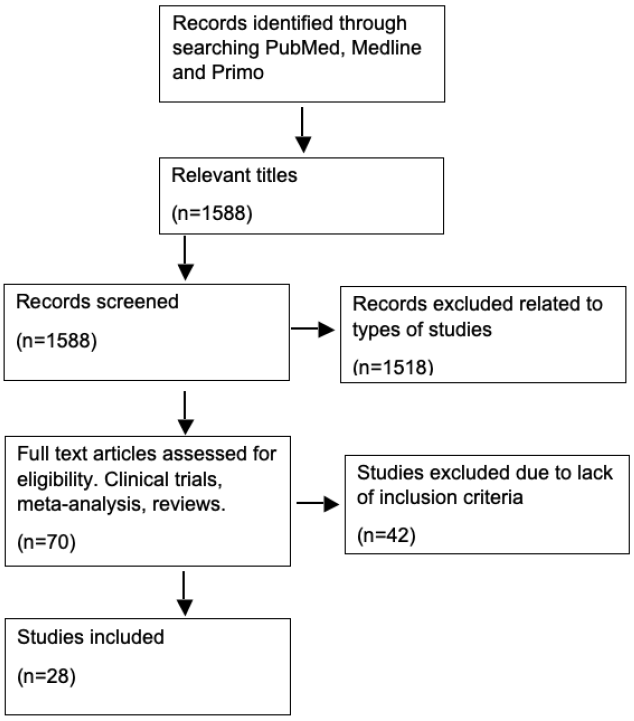

Figure 2. Flow chart of the search process.

Psychological wellbeing of patients

A study released in 2017 explored the short-term psychological impacts of silicone breast implants and DIEP flap surgery for breast reconstruction and found that both treatments had an impact on a patient's mental health.[6] It stated that patients who received implants showed decreased anxiety following surgery, most likely due to the immediate results that breast implants deliver, whereas DIEP flap surgery was associated with an increase in depressive symptoms following surgery.[6] It could be inferred that this is due to the higher levels of pain experienced by patients receiving autologous reconstruction and the scarring on the abdomen. The study explored the short-term psychological impacts of breast reconstruction with pre- and postoperative psychological questionnaires. The use of questionnaires increases reproducibility and reliability of these data as they allow a variety of responses from patients. They are, however, limited by response bias, where respondents may not answer questions truthfully. Limitations of using questionnaires can be overcome by ensuring anonymity (and ensuring participants are aware of this) and asking participants to complete the questionnaire within a short time-period post-operatively.[6]

> *In contrast, studies into the ongoing psychological well-being of patients have found that, in the long-term, patients are more satisfied with the outcomes of the DIEP flap than silicone breast implants.*[5,7–9]

This is supported by a study that reviewed patient satisfaction a year after either DIEP flap surgery or silicone implants for breast reconstruction following mastectomy. It was found that patients who had autologous reconstruction were more satisfied with their breasts a year after the surgery, having greater psychological and sexual well-being, as compared with women with breast implants.[8] It could, therefore, be argued that the long-term benefits of the DIEP flap outweigh the pain and poor mental health issues found in the short term. DIEP flaps are a newer form of breast reconstruction compared with breast implants,[5] so there are fewer studies that investigate the long-term psychological impacts of DIEP flap surgery. Further research into the psychological impacts of DIEP flap surgery is needed to accurately assess the ongoing psychological effects and influences of the two approaches.

Cost-effectiveness

Currently, in the NHS, silicone breast implants cost around £3,500-£7,000 per patient,[10] marginally less than the £10,000 cost of the DIEP flap.[11] However, evidence suggests that, in the long term, DIEP flap reconstruction is more cost-effective.[9,12] Patients receiving breast implants have high rates of complications and surgical revisions compared with autologous reconstruction. The US Food and Drug Administration (FDA) stated that, after three years, 73% of women with breast implants experience a common complication, such as capsular contracture or a rupture requiring additional surgery.

Along with complications, breast implants are not a permanent form of reconstruction and need to be replaced approximately every ten years.[10,13] Due to the additional surgical revisions associated with breast implants,[13] along with the higher rates of long-term patient satisfaction following DIEP flap surgery, it has been argued that DIEP flap surgery is more cost-effective.[12]

Breast-implant-associated anaplastic large cell lymphoma

Evidence indicates that there is an associated risk between silicone breast implants and a form of cancer called breast-implant-associated anaplastic large cell lymphoma (BIA-ALCL).[10,14] BIA-ALCL was officially recognised as a subclass of anaplastic large cell lymphoma (ALCL) by the World Health Organization (WHO) in 2016.[14] BIA-ALCL is thought to occur when the body adversely reacts to the silicone in the breast implants,[15] leading to damage of the T cells in the immune system and surrounding breast tissue.[14,15] BIA-ALCL is symptomatic with swelling and pain in the breasts due to an implant-associated seroma that occurs more than one year after surgery.[14] This condition is commonly detected through the presentation of the above symptoms, combined with raised CD30, a tumour marker antigen.[16] If a patient is diagnosed with BIA-ALCL, the implant and surrounding breast tissue is removed.[16]

Case reports describe BIA-ALCL as a delayed seroma that develops typically in patients with a median age of 55 years and an interval

of implantation of 7 to 10 years (**Figure 3**).[17] One case describes the development of a palpable mass over four weeks in the left breast of a 68-year-old woman, on a background of mastectomy and breast reconstruction with textured implants 7 years previously. Ultrasound revealed a 300ml seroma, which required bilateral surgical resection of the implants.[17] This case is a typical presentation of a BIA-ALCL and highlights that textured implants are a risk factor for developing BIA-ALCL.

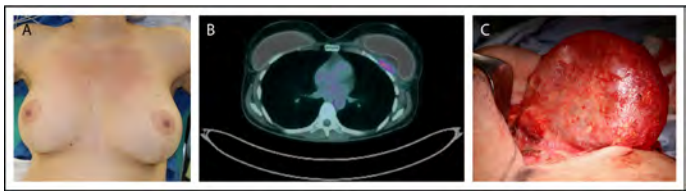

Figure 3. BIA-ALCL following breast reconstruction using silicone breast implants. (**a**) An image taken 7 years after cosmetic breast augmentation with bilateral textured breast implants. (**b**) Perioperative computerised tomography (CT) scan showing posterior capsule wall mass invading the chest wall (shown in pink). (**c**) Image showing a total capsulectomy with excision of skin involvement to ensure that any residual disease is removed and to reduce risk of disease progression. Republished with permission of Elsevier Science & Technology Journals, from Mehta-Shah et al;[17] permission conveyed through Copyright Clearance Center, Inc.

The rates of BIA-ALCL are shown to be increasing internationally. A report by De Jong et al (2008) stated the rate was 0.1-0.3 per 10,0000 patients in the Netherlands,[16] and the US FDA in 2017 reported an incidence of 0.6-1.2 per 100,000 in the USA.[18] As of 30th September 2018, the US FDA received 457 individual medical device reports (MDRs) of BIA-ALCL.[14] This data recognises a significant increase in the incidence of BIA-ALCL, which correlates to the increased number of silicone breast implant reconstructions performed. While MDRs provide a valuable source of information, it should be recognised that they do not give details about the patient's past medical history and are completed by doctors. Thus, this allows the generation of bias and false priors, whereby the doctors are more focussed on the detection of a specific condition.

Incident rates of BIA-ALCL may be difficult to calculate as the condition is rare and there is a lack of reporting and possible duplicate reporting; however, several countries, including France and the US, are taking BIA-ALCL very seriously. The French National Cancer Institute is considering a general ban on breast implants, and in 2015 the French Ministry of Health ordered all breast implants to come with a cancer warning.[14] However, it could be argued that, in doing this, the French Ministry is removing patient autonomy.

Capsular contracture with breast implants

A significant proportion of patients who have silicone breast implants need to have further surgery due to complications, such as capsular contracture. Capsular contracture is defined as a pathological process involving the contraction of the encapsulated scar tissue associated with the implant.[19] The condition can cause patients to have chest pain, as well as firmness and distortion of the breast.[19] Capsular contracture occurs due to a fibrotic reaction between the surrounding breast tissue and the silicone contained within the implant, although it should be noted that the exact mechanism is unclear.[20]

Capsular contracture is stated by the FDA to occur in 12.7% of primary reconstructions, with global rates of up to 45%.[21,22] A 10-year study into women receiving silicone breast implants in the US found that 24.6% of patients who received implant reconstruction developed capsular contraction.[23] Patients are commonly treated by the removal of the breast implant and affected scar tissue.[14] Not only does this incur further pain and discomfort for the patient, but it also increases NHS costs and lengthens time spent in hospital.

Further research has been carried out exploring the medical management of capsular contracture with pirfenidone (PFD).[17] As an anti-inflammatory and antifibrotic agent, PFD acts to reduce inflammation, contracture and capsule thickness when used for eight weeks. The Baker classification is a system commonly used to grade capsular contracture.[17] A 2016 literature review demonstrated that, in cases of capsular contracture with Baker Grade III, anti-inflammatory medications can be used and in three months patients are re-classified as Baker Grade I.[24] As surgical management is typically reserved for cases of capsular contracture with Baker Grade III or VI, PFD could be an intervention that reduces the necessity for surgical management in some severe cases of capsular contracture.[17]

Length of stay of patients in hospital

For patients receiving silicone breast implants, the surgery time is 60-90 minutes, with many patients being able to go home the same day.[4] As well as this, breast implantation is a relatively simple procedure and can be carried out by a number of surgeons.[5] In comparison, the DIEP flap is a form of microsurgery and, thus, can only be carried out by surgeons with training in microsurgery.[25] DIEP flap surgery can take 6-8 hours, and patients are required to stay in the hospital for 5-8 days.[5] The specialist skills required for DIEP flap surgery means it is less available to patients compared with breast implants.

> *While the DIEP flap surgery and associated hospital length of stay are longer, the breast reconstruction is permanent and does not need to be repeated, provided there are no complications. In contrast, breast implants last around ten years before they are required to be replaced,[13] and there may be complications before this that lead to the removal of the implant pre-term.[13]*

A report summarises this, stating that the mean number of surgical revisions for breast implants is 1.5 days compared with 0.8 days for DIEP flap.[11] Considering this, it could be surmised that, whilst the length of stay in the hospital is longer with the DIEP flap surgery in the short term, the overall length of hospital stay is not significantly different between the two procedures. However, it is important to recognise that complications can arise from DIEP flap reconstruction that lead to an extended length of hospital stay. A study reviewed 737 breast cancer patients who had autologous breast reconstruction, either immediately following mastectomy or after a period of time.[26] It showed that with immediate reconstruction, there is a greater risk of developing haematomas and seromas, whereas with delayed reconstruction, there is a greater association with wound problems.[26] Furthermore, bilateral DIEP flap breast reconstruction is a more risky procedure than unilateral reconstruction, with twice as many postoperative complications, primarily due to venous congestion, requiring reoperation.[27]

Conclusion

Reconstruction of the breasts is a major part of many women's pathway to recovery following mastectomy. Silicone breast implants offer women immediate satisfaction with their breasts in a quicker surgical procedure, at a smaller cost to the NHS.[10–12] However, complications can arise from breast implants, including BIA-ALCL and capsular contracture. Both conditions are treated by the removal of the implant and the surrounding tissue, leading to further physical pain and mental distress to the patient.[14,20]

In comparison, DIEP flap surgery is a much longer surgery and a more

expensive form of breast reconstruction.[5,11] Patients are required to remain in the hospital for 5-8 days and many experience depressive symptoms in the short term.[5] This considered, the DIEP flap has been shown to provide greater overall patient satisfaction in the long term.[7] It is a procedure with fewer associated complications and a history of requiring fewer surgical revisions.[7] Arguably, these factors outweigh the short-term disadvantages (see **Table 1**).

Table 1. Comparison of DIEP flap surgery with silicone breast implants for patients seeking breast reconstruction following mastectomy.

	DIEP flap	Breast implants
Impact on patients' mental health	Can be detrimental to mental health in the short term.[7] Have high levels of satisfaction in the long term.[8]	Good mental health outcomes in short term.[7] Have slightly lower levels of satisfaction in the long term.[8]
Risk of developing cancer	DIEP flap surgery does not involve the use of silicone thus avoids risk of BIA-ALCL.	Small risk of developing BIA-ALCL from silicone breast implants.[14,18]
Lifespan of reconstruction	DIEP flap breast reconstruction is a life-long solution.[4,13]	Silicone breast implants need to be replaced every ten years.[4,13] Increased incidence of surgical revisions required in breast implants.[27]
Hospital length of stay	Length of stay in hospital is longer for patients receiving the DIEP flap than for those receiving breast implants.[10]	Breast implants have higher rates of surgical revision, making the length of stay less significant.[13]
Cost to the NHS	It is suggested that DIEP flap surgery is more cost effective in the long term. This is evident when the case of additional surgeries and medical interventions are taken into account.[12,16]	Initial surgery using breast implants is cheaper.[12]

Additional case studies exploring the long-term outcomes of DIEP flap reconstruction are needed to support the replacement of breast implants by DIEP flap surgery in the NHS. There should be a focus on complications, expense, and patient-perceived outcomes. To help reduce the limitations of cohort bias and increase the reliability of data, where possible, studies should be carried out on large cohorts. However, based on the research conducted for this review, it is suggested that DIEP flap surgery is a more beneficial form of breast reconstruction, compared with silicone breast implants. DIEP flap reconstruction is also more cost-effective for the NHS in the long term, indicating a possible way for the NHS to deliver more satisfactory patient care at a lower cost.

Contribution statement: The above literature review is the sole work of the author; the author contributed to the design and content and gave final approval of the above review to be included in Inspire.

References

1. Koçan S, Gürsoy A. Body Image of Women with Breast Cancer After Mastectomy: A Qualitative Research. J Breast Health. 2016;12(4):145–50.
2. Glicenstein J. History of augmentation mammaplasty. Ann Chir Plast Esthet. 2005;50(5):337–49.
3. Ooi AS, Song DH. Reducing infection risk in implant-based breast-reconstruction surgery: challenges and solutions. Breast Cancer Dove Med Press. 2016;8:161–72.
4. Fardo D, Sequeira Campos M, et al (2021). Breast Augmentation. Available from: www.ncbi.nlm.nih.gov/books/NBK482206/. Accessed: 18 April 2021
5. Hamdi M, Rebecca A. The Deep Inferior Epigastric Artery Perforator Flap (DIEAP) in Breast Reconstruction. Semin Plast Surg. 2006;20(2):95–102.
6. Gopie JP, Timman R, Hilhorst MT, et al. The short-term psychological impact of complications after breast reconstruction. Psychooncology. 2013;22(2):290-298.
7. Sgarzani R, Negosanti L, Morselli PG, et al. Patient Satisfaction and Quality of Life in DIEAP Flap versus Implant Breast Reconstruction. Surg Res Pract. 2015;2015:405163.
8. Pusic AL, Matros E, Fine N, et al. Patient-Reported Outcomes 1 Year After Immediate Breast Reconstruction: Results of the Mastectomy Reconstruction Outcomes Consortium Study. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(22):2499–506.
9. Lagares-Borrego A, Gacto-Sanchez P, Infante-Cossio P, et al. A comparison of long-term cost and clinical outcomes between the two-stage sequence expander/prosthesis and autologous deep inferior epigastric flap methods for breast reconstruction in a public hospital. J Plast Reconstr Aesthetic Surg. 2016;69(2):196–205.
10. NHS (2017) Cosmetic surgery - Breast enlargement (implants). Available from: www.nhs.uk/conditions/cosmetic-procedures/breast-enlargement/. Accessed: 11 April 2019
11. Atherton DD, Hills AJ, Moradi P, Muirhead N, Wood SH. The economic viability of breast reconstruction in the UK: comparison of a single surgeon's experience of implant; LD; TRAM and DIEP based reconstructions in 274 patients. J Plast Reconstr Aesthetic Surg, 2011;64(6):710–5.
12. Matros E, Albornoz CR, Razdan SN, et al. Cost-effectiveness analysis of implants versus autologous perforator flaps using the BREAST-Q. Plast Reconstr Surg. 2015;135(4):937–46.
13. Goodman CM, Cohen V, Thornby J, et al. The life span of silicone gel breast implants and a comparison of mammography, ultrasonography, and magnetic resonance imaging in detecting implant rupture: a meta-analysis. Ann Plast Surg. 1998;41(6):577–85; discussion 585-586.
14. US Food & Drug Administration (2019) Questions and Answers about Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Available from: www.fda.gov/medical-devices/breast-implants/questions-and-answers-about-breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl. Accessed: 31 March 2019.
15. Bizjak M, Selmi C, Praprotnik S, et al. Silicone implants and lymphoma: The role of inflammation. J Autoimmun. 2015;65:64–73.
16. Breastcancer.org (2019) DIEP Flap Reconstruction: What to Expect. Available from:www.breastcancer.org/treatment/surgery/reconstruction/types/autologous/diep/what-to-expect. Accessed: 31 March 2019
17. Mehta-Shah N, Clemens MW, Horwitz SM. How I treat breast implant–associated anaplastic large cell lymphoma. Blood. 2018;132(18):1889–98.
18. Ezekwudo DE, Ifabiyi T, Gbadamosi B, et al. Breast Implant–Associated Anaplastic Large Cell Lymphoma: A Case Report and Review of the Literature. Case Rep Oncol Med. 2017;2017:e6478467.
19. Gampper TJ, Khoury H, Gottlieb W, et al. Silicone gel implants in breast augmentation and reconstruction. Ann Plast Surg. 2007;59(5):581–90.
20. Vieira VJ, D'Acampora A, Neves FS, et al. Capsular Contracture In Silicone Breast Implants: Insights From Rat Models. An Acad Bras Cienc. 2016;88(3):1459–70.
21. Coroneos CJ, Selber JC, Offodile AC, et al. US FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients. Ann Surg. 2019;269(1):30–6.
22. El-Sheikh Y, Tutino R, Knight C, et al. Incidence of capsular contracture in silicone versus saline cosmetic augmentation mammoplasty: A meta-analysis. Can J Plast Surg J Can Chir Plast. 2008;16(4):211–5.

23. Spear SL, Murphy DK. Natrelle round silicone breast implants: Core Study results at 10 years. Plast Reconstr Surg. 2014;133(6):1354–61.
24. Malahias M, Jordan DJ, Hughes LC, et al. A literature review and summary of capsular contracture: An ongoing challenge to breast surgeons and their patients. International Journal of Surgery Open. 2016;1;3:1–7.
25. Lhuaire M, Hivelin M, Dramé M, et al. Determining the best recipient vessel site for autologous microsurgical breast reconstruction with DIEP flaps: An anatomical study. J Plast Reconstr Aesthetic Surg JPRAS. 2017;70(6):781–91.
26. Wade RG, Razzano S, Sassoon EM, et al. Complications in DIEP Flap Breast Reconstruction After Mastectomy for Breast Cancer: A Prospective Cohort Study Comparing Unilateral Versus Bilateral Reconstructions. Ann Surg Oncol. 2017;24(6):1465–74.
27. Beugels J, Bod L, van Kuijk SMJ, Qiu SS, et al. Complications following immediate compared to delayed deep inferior epigastric artery perforator flap breast reconstructions. Breast Cancer Res Treat. 2018;169(2):349–57.

Review

Is exercise a valuable method of preventing feelings of anxiety and depression in 16–21-year-olds during the COVID-19 lockdown?

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Abstract

The Coronavirus 2019 (COVID-19) pandemic has brought government enforced quarantine on many countries including the UK. One of the only permitted reasons to leave the home was exercise. A breakdown in normal routines has already caused a spike in online searches related to anxiety and depression. This is relevant to the 16-21 year age group as support systems that usually present in post-16 or higher education or workplaces are removed and feelings of disappointment at missing out on rites of passage are experienced. During lockdown, exercise both outdoors and at home via online workouts increased, with the combination of social interaction and physical activity providing a coping tool. The social facilitation theory provides insight into the mechanisms for prevention of feelings of anxiety and depression through exercise. It is vital for public health to continue the promotion of exercise at home during lockdowns and beyond to enable people to keep up their new regimes.

Abbreviations

COVID-19 – Coronavirus 2019
GPs – General practitioners

Introduction

At the time of writing Coronavirus 2019 (COVID-19) has claimed over 228,000 lives and infected a further 3 million people. With 211 countries having cases and the WHO declaring pandemic status on 11th March 2020, the virus has been cited the biggest global event since World War II.[1] Following the closure of schools, universities, restaurants, gyms and other businesses in the days beforehand, the UK went under 'lockdown' measures on 23rd March 2020. On this day the prime minister laid out only 4 essential reasons for leaving the house.[2]

One of the permitted reasons for leaving the home was to participate in one form of outdoor exercise per day, choosing from walking, cycling or running. In the six weeks since enforcement, a perceptible increase in people exercising has not escaped the notice of both the public and press. This is coupled with a mass drive towards home workouts, be these self-directed, using recorded video or in live format. A pertinent example of home workouts being taken up are those by the personal trainer Joe Wicks, who set out to provide 'PE classes for the Nation' at 9am on weekdays. His live follow along at home workouts received 23 million views in the first week, with each subsequent session receiving between 500,000 to 1 million views to date.[3]

It is commonly accepted that exercise is a vital part of a healthy lifestyle, with many now recognising the benefits on mental as well as physical health.

> *In England, NICE recommend healthcare professionals to consider exercise as a preventative measure for depression as well as physical health problems such as cardiovascular disease.*[4]

During an unprecedented time where isolation is the norm, loneliness is potentially at an all-time high,[5] which is a predisposing factor for feelings of anxiety and depression. Perhaps a combination of the instantaneity of social media and the community feel of exercise could be considered as a protection against the development of symptoms of depression and anxiety.

A group of interest during these times of restrictions is young adults aged 16-21 years; without the structure and activity of secondary school, college or university how does one cope with potential mental health problems? With these institutions usually providing support in forms of socialising, pastoral care and on-site counselling services where do young adults now turn to cope with symptoms of anxiety or depression?[6] Many of those not in education have been furloughed or are working from home instead of going into the work place, also leading to breakdown in routine and support systems.[7]

Compared to other demographics, arguably this group is missing out the most socially at an important stage of development between adolescence and adulthood.[6,7] This group is in a time of life when usually the first tastes of independence and autonomy begin which usually would bring excitement and a sense of belonging to the more 'grown up' world of college, university or work. Due to lockdown much of this has been lost. For instance, many key milestones such as exams, graduations and similar 'coming of age' celebrations have been cancelled.[7]

Data search

The PubMed database was used to find relevant literature relating to exercise and specific mental health symptoms. The search terms were 'exercise' or 'physical activity' and these had to be included in the title or abstract. 'Anxiety' or 'depression', and 'young adult' or 'adolescent' and 'prevention' also had to be included in the title or abstract of papers. The operatives 'and' and 'or' were used.

Information relating to quarantine measures and their psychological effects on young adults was found using the same search technique. In addition, papers on coronavirus, social isolation and quarantine were sourced from PubMed and the Lancet. General news and opinion pieces in the media were also used due to the nature of the pandemic in current affairs and lack of well-established scientific reviews as the virus and the response of the government and healthcare is rapidly evolving. As the issues at hand are so new, grey literature was a prominent source. A similar strategy was used to collate data on exercise and physical activity during this time.

The sources of information were chosen based on relevance by reading abstracts of the papers brought up by the search terms. Those that focused on populations with other existing chronic diseases that were not mental health related were excluded.

Lockdown and mental health

With normal delivery by school and universities suspended in 188 countries, 1.5 billion young people are out of education and therefore the routine provided by these institutions.[6] The negative psychological effects of these social isolation and quarantine measures are perhaps more profound than expected, including symptoms of anxiety and depression which could possibly continue into later life after quarantine measures end.[7]

A recent paper highlights the need for novel interventions to protect mental wellbeing in COVID-19, including prosocial behaviour and optimising online resources.[8] Exercise at home in a virtual group would fulfil these criteria and is therefore a valuable option. The researchers also emphasised the negative outcomes of quarantine, including self-harm and suicide as well as psychosocial risks such as social disconnection, entrapment and bereavement.[8]

To examine the psychological and emotional effects of social distancing and isolation Young Minds released a survey of 2111 people aged 16-25 years in the UK. 83% of those with mental illness said their symptoms had been worsened by the pandemic. Out of all the participants, 60% cited exercise as an activity that was helpful for their mental health. Factors such as the breakdown of routine, change in living and financial circumstances, strained relationships, and missing family and friends could be catalysts in this situation.[6] These are compounded by reduced access to support from primary care and counselling or therapy services.[5]

> *An article on Medium stated Google searches including the terms 'anxiety' and 'depression' along with 'coronavirus' increased drastically during quarantine.[9]*

This trend is backed up in the focus population by the findings of the Teenagers' Experiences of Life in Lockdown study.[7] Underpinning the mechanism associated with symptoms of worsened mental health is vital to ascertain preventative measures and, in this case, to determine how valuable exercise may be.

A review of 24 papers investigating the psychological impact of quarantine saw symptoms of post-traumatic stress in most articles. Other effects included frustration and fear of infection. Response to stressors such as inadequate supplies, financial strain and too little or too much information was cited as a source of these negative feelings.[10] Through this study it was decided that effective and rapid communication was essential, and public health should draw attention to the altruism of self-isolating when this is done by choice. However, as the present quarantine is imposed by the government, the study predicts more long-term complications and higher distress levels than with voluntary self-isolation. This is pertinent to the present topic as stress tends to precipitate feelings of anxiety and depression.[8]

Exercise and feelings of anxiety and depression

Steptoe and Butler have been carrying out seminal research in this area in adolescents since the 1990s. This group was able to identify a dose response relationship between exercise and improved mental health.[11] This has been supported in more recent research; for example in a systematic review on overall health in adolescents, mental health was one of the factors most impacted by exercise interventions.[12] The strongest evidence gathered by the study was related to the short term benefits on mental health. It was concluded that exercise promotion should begin at a young age to ensure health benefits in adulthood. Another systematic review of cohort studies found consistent evidence to support a negative association between physical activity and depression in the future in 25 out of 30 studies examined.[13]

Another study in the USA between 2011 and 2015 found modality of exercise was not important, as any type of exercise was seen to provide a lower mental health burden.

> *Although all modalities of exercise were beneficial, participation in team sports resulted in the largest reduction in mental health burden, which was 22.3% lower than with no exercise participation.[14]*

This was measured by self-recorded days of poor mental health, which means the results are reliant on subjective measures.

The relationship between exercise and stress is also important to

investigate, due to the distressing nature of quarantine. Taking this into account, a comparative trial of law students (chosen as a 'stressed' group) supported increased physical activity having a protective effect against symptoms including stress, anxiety and depression.[15] This correlation was found to be stronger than in a less stressed group of students. However, level of exercise intensity was not recorded, only frequency. Students who exercised more often also reported stronger feelings of 'belonging' in their university community. Further social benefits were identified as well as psychological effects. In a review of 30 studies conducted between 1990 and 2012 by Eime *et al*., multiple psychological and social health benefits were recorded, with the most universal being raised self-esteem, followed by reduced symptoms of depression.[16] The positive relationship between exercise participation and self-esteem in the target demographic is supported by the findings of many research groups.[16,17]

Social value of exercise

Social facilitation is the process by which an individual's performance is improved by the act of being part of a team doing the same activity.[18] For example, studying in a library may be more productive, due to the motivation of being surrounded by others doing the same thing. Participating in a live workout class can be more enjoyable due to the element of motivation social facilitation provides.[19]

Eime *et al*., also found that team sports were associated with better mental health outcomes as opposed to individual exercise, because of the social nature of the activity.[16,19] This highlights the social value of live workouts under quarantine measures, as an atmosphere similar to team sport is cultivated. This can be helpful during a time when you cannot spend any time with people outside of your own household, let alone a sports team.

Furthermore, it is recognised that social relationships form a buffer during distressing events.[8] In a recent paper, Lippi *et al*. tentatively recommended increased social connections via social media and smartphones during lockdown.[20] Interactive virtual exercise would fulfil this due to 'live comments/chat' features on livestreaming platforms. Their hesitancy in recommendation comes from existing negative associations between social media and mental health.[20] Researchers stated remedies should be readily put into action, something that has seen promotion by Sport England in their 'Stay in Workout' campaign.[21,22] This aims to promote healthy and safe introduction to exercise, with warm up and recovery advice. A social media hashtag for people to share their experience and motivate others is also provided.[22] By these modalities, exercise could provide a combination of digital connectivity, purpose and self-esteem necessary for prevention of negative psychological states such as loneliness, depression and anxiety.

Other benefits of xercise in lockdown

Exercise participation could be increased during this time as barriers are removed, such as cost of a gym membership, feeling judged or out of place in a typical gym setting or exercising outdoors and avoiding cold weather. There is often no equipment or membership needed.[23]

Further to the aforementioned mechanisms, exercise contributes to a symbiotic relationship with other healthy behaviours such as healthy eating and sleeping well. This leads to overall improved mental health, and protection from negative psychological effects of social isolation. However, in studies of social outcomes it is difficult to elucidate a causal link due to the multifaceted, multifactorial factors of health, such as home life, relationships and life events.[24]

Limitations of the present paper

There are shortcomings to this review because of the proximity in time of writing to the imposition of lockdown measures. This meant much information was anecdotal or transferred from studies relating to similar situations. Even one year after the time of writing the evidence available in the literature is likely to be less limited and more conclusive.

Conclusion

From the research reviewed we can see that exercise is a valuable intervention for prevention of mild to moderate symptoms of anxiety and depression in young people. Exercise can be considered valuable for this age group because of improved self-esteem and the sense of wellbeing that comes with this. Higher self-esteem and mental wellbeing can translate to fewer symptoms of anxiety and depression. Looking at the COVID-19 pandemic, the extent of the psychological impacts from the present quarantine measures in the UK and worldwide remains to be seen. However, undeniable positives have arisen from these trying times, an anecdotal uptake in home and outdoor exercise being one of them. Perhaps without the drive and allowance for participation in these activities, symptoms of depression and anxiety would be far more prevalent in the focus group. Looking forward, it is unknown how both healthcare professionals as individuals, and public health campaigns can carry forward this positive trend post-quarantine. Inevitably this time will come with challenges of its own.

> *Perhaps the success of participation in and psychological benefits experienced from live workouts in 16-21 year olds could become the cornerstone for a new method of exercise prescription from GPs.*

The NHS could provide live workouts on their website, or endorse other creators doing so. Patients at risk of mood disorders could be referred to participate. The mechanisms of these interventions are two pronged, firstly social interaction and secondly the physical act of moving the body, both resulting in reduced feelings of anxiety and depression.

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References

1. Hamid S, Mir MY, Rohela GK. Novel coronavirus disease (COVID-19): a pandemic (epidemiology, pathogenesis and potential therapeutics). New Microbes and New Infections. 2020;35:100679.
2. Nicola M, O'Neill N, Sohrabi C, et al. Evidence based management guideline for the COVID-19 pandemic - review article. International Journal of Surgery. 2020.
3. Evans M. Joe Wicks lands 1.2million new YouTube subscribers in one week as workout videos top 20million views: Metro; 2020. Available from: https://metro.co.uk/2020/04/01/joe-wicks-lands-1-2million-new-youtube-subscribers-one-week-12492592/. Accessed: 30 April 2020.
4. NICE. Physical activity: exercise referral schemes Public health guideline [PH54]: National Institute for Health and Care Excellence; 2014. Available from: https://www.nice.org.uk/guidance/ph54/chapter/What-is-this-guideline-about. Accessed: 30 April 2020.
5. Hiremath P, Suhas Kowshik CS, Manjunath M, et al. COVID 19: Impact of lock-down on mental health and tips to overcome. Asian Journal of Psychiatry. 2020;51:102088.
6. Lee J. Mental health effects of school closures during COVID-19. The Lancet Child & Adolescent Health; 2020; 4(6) 421.
7. Demkowicz O, Ashworth E, Hanley T, 2020. Teenagers' Experiences of Life in Lockdown (TELL). Available at: https://documents.manchester.ac.uk/display.aspx?DocID=50543. Accessed: 8 May 2021.
8. Holmes EA, O'Connor RC, Perry VH, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. The Lancet Psychiatry.
9. BioBeats. Mental health-related Google searches spike amid global lockdown: Medium; 2020. Available from: https://medium.com/@biobeats/mental-health-related-google-searches-spike-amid-global-lockdown-e3a8bbb9fe4.
10. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet. 2020; 395(10227):912-20.
11. Steptoe A, Butler N. Sports participation and emotional wellbeing in adolescents. Lancet. 1996; 347(9018):1789-92.
12. Hallal PC, Victora CG, Azevedo MR, et al. Adolescent physical activity and health: a systematic review. Sports Medicine. 2006; 36(12):1019-30.
13. Mammen G, Faulkner G. Physical activity and the prevention of depression: a systematic review of prospective studies. American Journal of Preventative Medicine. 2013; 45(5):649-57.
14. Chekroud SR, Gueorguieva R, Zheutlin AB, et al. Association between physical exercise and mental health in 1.2 million individuals in the USA between 2011 and 2015: a cross-sectional study. Lancet Psychiatry. 2018; 5(9):739-46.
15. Skead NK, Rogers SL. Running to well-being: A comparative study on the impact of exercise on the physical and mental health of law and psychology students. International Journal of Law and Psychiatry. 2016; 49(Pt A):66-74.
16. Eime RM, Young JA, Harvey JT, et al. A systematic review of the psychological and social benefits of participation in sport for children and adolescents: informing development of a conceptual model of health through sport. The International Journal of Behavioral Nutrition and Physical Activity. 2013; 10:98.
17. Kipp LE. Psychosocial aspects of youth physical activity. Pediatric Exercise Science. 2016; 28(1):28-31.
18. Hooper AEC. An evolutionary approach to understanding social facilitation: Energy expenditure and exercise motivation. 2013. University of New Mexico Digital Repository.
19. Gaz DV, Smith AM. Psychosocial benefits and implications of exercise. Archives of physical medicine and rehabilitation. 2012; 4(11):812-7.
20. Lippi G, Henry BM, Bovo C, et al. Health risks and potential remedies during prolonged lockdowns for coronavirus disease 2019 (COVID-19). Diagnosis. 2020.
21. Williams SN, Armitage CJ, Tampe T, et al. Public perceptions and experiences of social distancing and social isolation during the COVID-19 pandemic: A UK-based focus group study. MedRxiv. 2020:2020.04.10.20061267.
22. Sport England. Stay in, work out: Sport England; 2020. Available from: https://www.sportengland.org/stayinworkout#join_the_movement.
23. Kaye S. Cooped up? Approaches to at-home exercise. Companion Animal.0(0):1-5.
24. Meyer OL, Castro-Schilo L, Aguilar-Gaxiola S. Determinants of mental health and self-rated health: a model of socioeconomic status, neighborhood safety, and physical activity. American Journal of Public Health. 2014;104(9):1734-41.

Review

How does defensive medicine cause harm to patients in the healthcare environment?

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Abstract

This paper aims to explore defensive medicine (DM) in order to raise awareness of how it can cause harm. DM describes methods that healthcare professionals may use to avoid litigation. Raising awareness should hopefully deter healthcare professionals from these behaviours, such as over-prescribing antibiotics and ordering unnecessary tests, and achieve a better standard of care for patients. Improving this standard of care is something that healthcare professionals should always strive towards; however, they may stray from this as they adapt to the pressures of evolving healthcare practices. This topic is important as defensive practices are often carried out by healthcare professionals without realising the consequences. Sometimes it can be harmless, but often investigations are performed in medicine which reveal incidental findings. These could include blood test or scan results that may be harmless and unrelated to the patient's presentation. They often warrant unnecessary investigations and treatments due to concerns of low-risk differentials which may be best left untreated. At times, these approaches can cause unnecessary harm and should be avoided in the patient's best interests.

Abbreviations

AMR - Antimicrobial resistance
COVID-19 - Coronavirus (Sars-CoV-2) disease of 2019
CS - Caesarean section
DM - Defensive medicine
EmCS - Emergency caesarean section
OBGYN - Obstetrics and gynaecology
UR - Uterine rupture
WHO - World Health Organisation

Introduction

Sekhar and Vyas define defensive medicine (DM) as "departing from normal medical practice as a safeguard from litigation".[1] Examples of DM include ordering unnecessary investigations, and overuse of or mistreatment with antibiotics. A study of 800 doctors in Pennsylvania highlighted the lack of clinical reasoning in some of these decisions, with 92% of participants ordering diagnostic tests for assurance.[1] Recent legal pressures on healthcare professionals have contributed to an increased use of defensive methods, but many of these have been suggested to cause harm inadvertently.[1] This paper will explore DM in obstetrics and microbiology and analyse the evidence behind the ways DM can cause harm to patients. This will be explored through post-surgical caesarean section (CS) complications and antimicrobial resistance (AMR), respectively, as their modern relevance allows significant evidence to be available.

Defensive medicine and the rise in caesarean sections

It is suggested in recent studies that obstetrics and gynaecology (OBGYN) physicians are at high risk of litigation, with a study in France recording an average of 2.4 claims per OBGYN physician.[2] Saudi Arabia, being a less developed country, recorded that 24.6% of malpractice claims were towards OBGYN physicians.[3]

> *This cannot indicate a global trend of litigation against OBGYN physicians but highlights its presence in contrasting socioeconomic settings.*

The rise of defensive practices is reflected in an Israeli study of 117 OBGYN physicians, in which 87% revealed they are "more likely to offer Caesarean section, even in the absence of clear medical indication".[4] There is a limitation that those surveyed encompass only 10% of all Israeli OBGYN physicians;[4] however, this population may be suggestive of a trend of defensive CS use. The existence of defensive CS use is also seen in European countries, such as Romania, with 70% of 73 participants admitting to using CS defensively and 86.3% commenting on fear of litigation.[5] Although UK data is limited, a study by Bourne *et al*. has indicated that between 10-30% of 5116 surveyed OBGYN doctors have carried out a form of DM.[6] Although the rates of defensive CS in UK studies are vastly smaller than in the Romanian study, UK studies tend to have lower response rates, possibly due to the risk of litigation and its potential impact on the NHS.[5,6]

CS is commonly used to avoid antenatal complications associated with breech presentation,[7] such as neonatal morbidity, hence being a lower risk option to external manipulation of the foetus or attempting a natural vaginal birth.[8,9] As an invasive procedure, CS leads to uterine scarring and carries an increased infection risk. The uterine scar can tear in subsequent pregnancies, which can result in severe complications.[7] A study in the Netherlands reflected uterine rupture (UR) to be over six times more likely in vaginal birth after CS than in vaginal birth without a previous CS birth.[10] A 2012 UK case-control study, including over 600 participants who gave birth over a 13 month period, also highlighted an incidence of 2.1 URs per 1000 vaginal births post CS compared to 0.3 per 1000 vaginal births in those who elected for another CS.[11] Albeit a rare complication, UR can result in emergency hysterectomy and stillbirth; however, fortunately, URs often avoid maternal mortality,[12,13] with case fatality rates reported at 1.3% in the UK study by Fitzpatrick *et al*.[11] Furthermore, 15/159 women with UR had emergency hysterectomies, and 18 stillbirths occurred (at a rate of 124/1000 live births compared to the standard UK rate of 7.5/1000) as a result of UR.[11] It cannot be concluded that the risk of maternal mortality is low in all settings as it may be much more likely in developing countries. Overall, the potential complications of UR inflict physical harm on the mother alongside psychological harm, the latter being associated with the loss of an unborn child and the negative impact on one's body image following hysterectomy.[14] Not all individuals experiencing hysterectomy will feel this way; however, due to the associated risks of CS, it can be argued that the practice of defensive CS may cause more harm than it reduces when CS is not medically indicated.

Furthermore, CS itself carries significant psychological impacts such as post-traumatic stress. The likelihood of a negative impact is significantly increased in emergency CS (EmCS),[15] which may arise in the context of UR. A 2019 systematic review, including 22 countries, found that 55% and 73% of women in Sweden and Australia, respectively, experienced significant stress or trauma during or after EmCS.[15] This delivery method was also suggested to impact early relationships and breastfeeding with offspring, with a participant in one study in a 2019 review seeing breastfeeding as a necessity to make up for "failing to provide their daughter with a normal birth".[16] This theme of failure emerges again when discussing maternal birth experiences of EmCS, alongside themes of helplessness and fear, with a participant in a separate study in this review feeling a sense of failure with themselves and betrayal in "being cheated" of their ideal birth experience.[17] Finally, three studies within this review reported low self-esteem after EmCS with two of these also commenting on themes of emotional vulnerability and regret.[18-20] The systematic review on the whole has some, albeit recognised, limitations including cultural differences, small sample sizes and often unidentified indications for EmCS.[15] As a result of these limitations, the effects and relevance of the above conclusions may be disputable in the context of DM and UR.[15] Nonetheless, the potential impact of EmCS on maternal mental health is important to consider as a risk of DM.

> *Therefore, it is important that provisions for psychological support of mothers who have had CS are considered moving forward in the field of OBGYN.*

Defensive medicine's contribution to antibiotic resistance

In the World Health Organization's (WHO's) 2014 report, 5/6 regions recorded Staphylococcus Aureus and Escherichia Coli to be resistant to the standard antibiotics for treatment in 50% or more of patients with these infections.[21] There is the limitation that not all member nations contributed to the data, so the results may not be fully representative, but they highlight a worrying statistic. The use of broad-spectrum antibiotics can kill both invading pathogens and our body's useful commensal bacteria, due to their cellular similarities. Any surviving bacteria, pathogenic or commensal, can spread resistance genes and proliferate a population of resistant bacteria.[22] The disruption of commensal bacteria may also cause some to become pathogenic.[22] Overall, this may make the antibiotics used ineffective in future.

As the understanding of AMR has grown, antibiotic use has been strictly regulated. People with common infections are typically no longer prescribed antibiotics, and infections requiring antibiotics are taken in a moderated way to limit resistance risk.[23] Despite this, a study of 661 infectious disease and clinical microbiology specialists from 74 countries recorded that 85% of these specialists adopted defensive behaviours towards their own patients and 76.4% advised others to adopt DM behaviours. Defensive behaviours included: "prescribing unnecessary broad-spectrum antibiotics" and "prolonging antibiotic treatment durations".[24] The defensive use of antibiotics poses a risk to patients as it promotes resistance which may reduce the options for treatment of bacterial infections. This indirectly causes harm to patients as these defensive actions increase the difficulty of treatment for hospital patients in the future and may lead to prolonged suffering. This is not true for all bacterial infections as there are many options for treatment, and some bacteria are yet to develop resistance, so there is not an immediate risk to the world population. However, a continuation of current trends poses risk as global deaths due to AMR have been predicted to rise to 10 million deaths a year by 2050.[25]

Even as recent as 2020, DM behaviours have arisen in the Coronavirus (Sars-CoV-2) disease of 2019 (COVID-19)pandemic, raising concern for acceleration of AMR. Despite COVID-19 being a viral disease, a review of COVID-19 cases in Asia reports that antibiotics were used to cover co-existing bacterial infections in 70% of cases, although only 10% had confirmed bacterial co-infections.[26] The fear and uncertainty surrounding this relatively new disease, and its associated rapid clinical decline in some patients, was likely a source of many lapses of clinical reasoning which may have had lasting effects on AMR.[27] However, there is a lot to learn from this pandemic regarding antibiotic stewardship; this term describing the supervised safe use of antibiotics.[25] The pandemic has shown how the achievability of

stewardship can change in the face of crisis. Under the strain of this new health challenge, the priority of AMR fell and only begins to rise again as the world recovers. The WHO suggests improved awareness of AMR could contribute to the management of DM in microbiology.[21] As new research emerges, it is likely the COVID-19 pandemic will be a great source of awareness and will motivate earlier intervention of microbiology policy and guidance if such another health crisis arises. Tackling it indirectly by reducing the incidence of infection is also suggested.[28] In summary, DM cannot be argued as a cause for AMR but its contribution to AMR poses additional and unnecessary risks to those bacterially infected in the future.

Discussion and conclusion

The cases discussed here are linked by being examples of positive DM, where a practitioner causes involuntary harm whilst attempting to prevent it. This may occur out of compassion, although cases in favour of convenience are where the issue of DM lies. One management option for this is tort reform. Tort reform is a collection of changes to civil justice law through which legal governing bodies aim to reduce the risk of litigation against doctors and discourage the need for DM practices. With this reform in place, legal bodies can attempt to limit patients making unjustified claims and place financial caps on the amount that can be claimed by victims of malpractice.[29,30] It is suggested that it may "significantly reduce… use of high-cost tests and treatments that do little to benefit patients."[29] In a systematic review of 37 articles, tort reform on non-economic damages, such as the psychological impacts of malpractice, was found to decrease DM practices and healthcare spending but did not affect quality of care. Otherwise, there was insufficient evidence on other types of tort reform.[30] However, the evidence base for tort reform is limited and lacks explicit data; trialling of tort reform in a range of countries may explore the potential benefit and risks of its use, and further research should expand the evidence base.

> *I believe that other potential recommendations to address DM surround education and support.*

Regarding education, it is clear from the evidence base that the understanding of the risks of these defence practices is quite high. However, this is underrepresented in clinical practice which may be due to limited awareness or priority of DM and its risks. Education may be beneficial for three audiences; firstly, educating medical students as part of the curriculum should act as a deterrent but also encourage them to be stewards to deter others; secondly, educating healthcare professionals during ward teaching, through application of clinical guidelines, and in their reflective practice should ensure that their stewardship and knowledge develops in training; and finally, education of the public in this practice should allow them to be more involved in shared decision making through allowing them to discuss these risks. This may be a source of controversy, but if delivered with reliable data and not with a fear-mongering manner it should act as a source of some empowerment for patients.

Regarding support, it is suggested that DM may arise in situations of uncertainty. I believe this could be addressed through two means; the first, which may come with education, is to destigmatise and encourage discussion of DM between healthcare staff. This could help reduce feelings of helplessness by normalising discussion of these legal concerns. Secondly, advice on ethical and medicolegal matters should be made more accessible. This could be through introducing on-site advisors or by raising awareness of what is currently available by inviting representatives of local or national medicolegal bodies to discuss their support services. This should discourage DM practices by encouraging healthcare professionals to discuss their concerns more readily before making unwise decisions that lack clinical reasoning.
There is a limitation that this article only indicates the long-term risks of DM, although there is remaining uncertainty as to the risks of DM in the short term. I believe that the short-term risks are a topic of concern as they may require more immediate action. It would be beneficial to analyse the evidence surrounding these short-term risks of DM, as publicising this may contribute to reducing their incidence. In addition, this review does not explore the patient perspective of DM. This is an important area for further research in order to contextualise the impacts of this practice.

In summary, the evidence suggests that DM may cause harm to patients in the healthcare environment through exposing them to long-term complications for the benefit of positive outcomes in the short term and reduction of legal liability. By straying from clinical guidelines or typical clinical reasoning, healthcare professionals can provide themselves and patients reassurance and a greater sense of wellbeing. In situations of uncertainty, healthcare professionals may feel helpless and as a result may not consider the long-term impacts of their actions when making decisions to relieve their uncertainty. Importantly, this does not suggest that these individuals are immoral people but may often be individuals who themselves are scared in the same way that patients may be in uncertain situations. Therefore, introduction of structured education and support surrounding DM and associated ethical and legal concerns may provide an effective solution to a topic that is unnecessarily taboo in nature.

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

References

1. Sekhar M, Vyas N. Defensive medicine: A bane to healthcare. Annals of Medical and Health Sciences Research, 2013; 3(2):295-296
2. Shojai R, Bretelle F, D'Ercole C et al. Analyse de la sinistralité en gynécologie-obstétrique: expérience d'un CHU en France. Journal de Gynécologie Obstétrique et Biologie de la Reproduction, 2013; 42(1):71-75.
3. AlDakhil L. Obstetric and gynecologic malpractice claims in Saudi Arabia: Incidence and cause. Journal of Forensic and Legal Medicine, 2016; 40:8-11.
4. Asher E, Dvir S, Seidman D et al. Defensive Medicine among Obstetricians and Gynecologists in Tertiary Hospitals. PLoS ONE, 2013;8(3):e57108.
5. Ionescu C, Dimitriu M, Poenaru E et al. Defensive caesarean section: A reality and a recommended health care improvement for Romanian obstetrics. Journal of Evaluation in Clinical Practice, 2018; 25(1):111-116.
6. Bourne T, Shah H, Falconieri N et al. Burnout, well-being and defensive medical practice among obstetricians and gynaecologists in the UK: cross-sectional survey study. BMJ Open, 2019; 9(11):e030968.
7. NHS (2018) Caesarean section. Available from: [https://www.nhs.uk/conditions/caesarean-section/]. Accessed [16 November 2018].
8. Hofmeyr G, Hannah M, Lawrie T. Planned caesarean section for term breech delivery. Cochrane Database of Systematic Reviews, 2001; (1)
9. Hannah M, Hannah W, Hewson S et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. The Lancet, 2000; 356(9239):1375-1383.
10. Zwart J, Richters J, Öry F et al. Uterine rupture in the Netherlands: a nationwide population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology, 2009; 116(8):1069-1080.
11. Fitzpatrick K, Kurinczuk J, Alfirevic Z et al. Uterine Rupture by Intended Mode of Delivery in the UK: A National Case-Control Study. PLoS Medicine, 2012; 9(3):e1001184.
12. Yap O, Kim E, Laros R. Maternal and neonatal outcomes after uterine rupture in labor. American Journal of Obstetrics and Gynecology, 2001; 184(7):1576-1581.

References

13. Gupta A, Nanda S. Uterine rupture in pregnancy: a five-year study. Archives of Gynecology and Obstetrics, 2010; 283(3):437-441.
14. Pinar G, Okdem S, Dogan N et al. The effects of hysterectomy on body image, self-esteem, and marital adjustment in Turkish women with gynecologic cancer. Clinical Journal of Oncology Nursing, 2012; 16(3):99-104.
15. Benton M, Salter A, Tape N et al. Women's psychosocial outcomes following an emergency caesarean section: A systematic literature review. BMC Pregnancy and Childbirth, 2019; 19(1).
16. Beck CT, Watson S. Impact of birth trauma on breast-feeding: A tale of two pathways. Nursing Research, 2008; 57(4):228–36.
17. Shorten A, Shorten B, Kennedy HP. Complexities of choice after prior cesarean: a narrative analysis. Birth: Issues in Perinatal Care, 2014; 41(2):178–84.
18. Carquillat P, Boulvain M, Guittier MJ. How does delivery method influence factors that contribute to women's childbirth experiences? Midwifery, 2016; 43:21–8.
19. Loto OM, Adewuya AO, Ajenifuja OK, Orji EO, Owolabi AT, Ogunniyi SO. The effect of caesarean section on self-esteem amongst primiparous women in South-Western Nigeria: a case-control study. Journal of Maternal-Fetal and Neonatal Medicine, 2009; 22(9):765–9.
20. Loto OM, Adewuya AO, Ajenifuja OK, Orji EO, Ayandiran EO, Owolabi AT, Ade-Ojo IP. Cesarean section in relation to self-esteem and parenting among new mothers in southwestern Nigeria. Acta Obstetricia et Gynecologica Scandinavica, 2010; 89(1):35–8.
21. World Health Organisation (2014) Antimicrobial resistance: global report on surveillance. Available from: [http://apps.who.int/iris/bitstream/handle/10665/112647/WHO_HSE_PED_AIP_2014.2_eng.pdf;jsessionid=FE7C1F029833CFBEEC8E39ED14BCF2D8?sequence=1]. Accessed [12 November 2018].
22. Summers A. Generally Overlooked Fundamentals of Bacterial Genetics and Ecology. Clinical Infectious Diseases, 2002; 34(3):85-92.
23. NICE (2018) Summary of antimicrobial prescribing guidance - managing common infections. Available from: [https://www.nice.org.uk/media/default/about/what-we-do/nice-guidance/antimicrobial%20guidance/summary-antimicrobial-prescribing-guidance.pdf]. Accessed [13 November 2018].
24. Tebano G, Dyar O, Beovic B et al. Defensive medicine among antibiotic stewards: the international ESCMID AntibioLegalMap survey. Journal of Antimicrobial Chemotherapy, 2018; 73(7):1989-1996.
25. Wellcome Trust (2016) Review on Antimicrobial Resistance. Tackling drug-resistant infection globally: final report and recommendations. Available from: [https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf]. Accessed [13 November 2018]
26. Rawson T, Moore L, Zhu N et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clinical Infectious Diseases, 2020; 71(9):2459-2468.
27. Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. BMJ, 2020; (8249)
28. World Health Organisation (2018) Global action plan on AMR. Available from: [http://www.who.int/antimicrobial-resistance/global-action-plan/en/]. Accessed [14 November 2018].
29. Hermer L, Brody H. Defensive Medicine, Cost Containment, and Reform. Journal of General Internal Medicine, 2010; 25(5):470-473.
30. Agarwal R, Gupta A, Gupta S. The impact of tort reform on defensive medicine, quality of care, and physician supply: A systematic review. Health Services Research, 2019; 54(4):851-859.

Research Highlights

When it rains it pours: one patient, three dental anomalies

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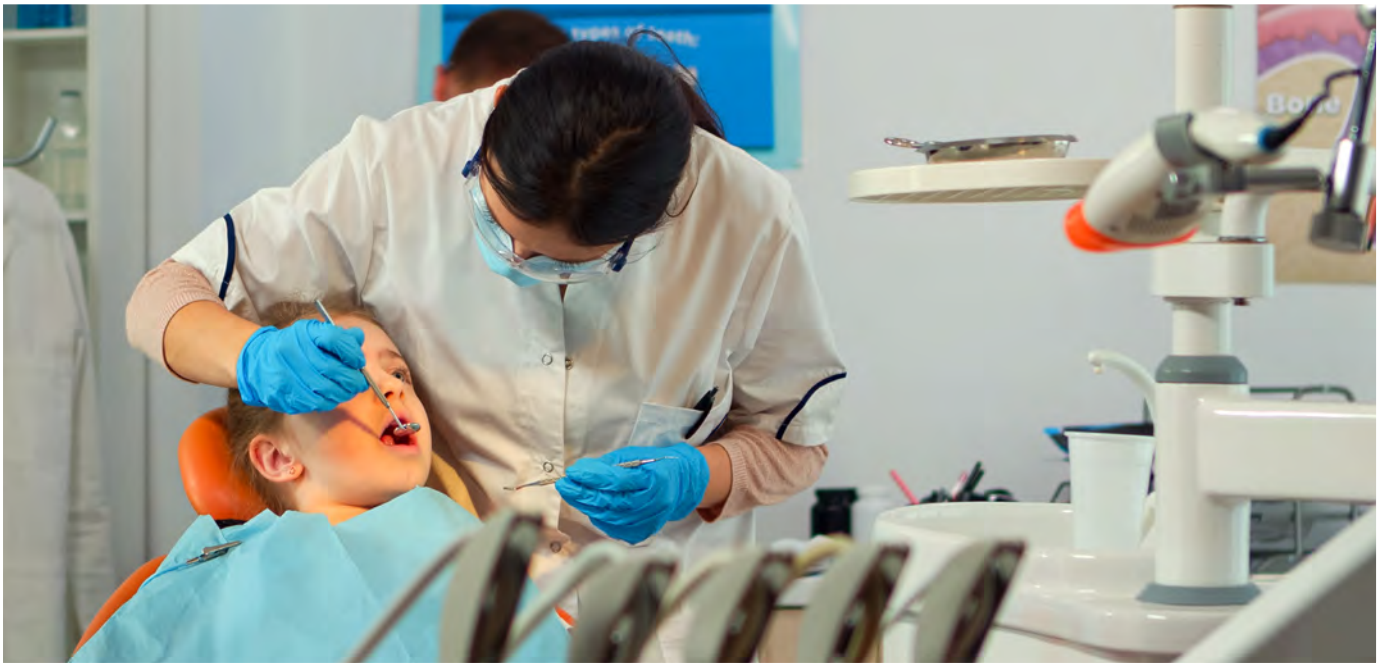

Abstract

Dentinogenesis imperfecta (DI) may present with a broad spectrum of dental and systemic manifestations and can be related to several anomalies. This case report describes a patient with the uncommon triad of DI Type 2 (bulbous crowns with pulp chambers obliteration), impacted upper first permanent molars (FPM) and severe hypodontia. This paper outlines the aetiology of the described dental anomalies and the available treatment options. It underlines the importance of a holistic approach, highlighting the clinical and psychological complexities in treating such patients, and demonstrates the need to seek specialist opinion and input from the interdisciplinary team. It also discusses how early intervention can resolve the functional and aesthetic problems caused by dentinal defects and thereby improve patients' quality of life.

Abbreviations

DEJ - Dentine-enamel junction
DGP - Dentin glycoprotein
DI - Dentinogenesis imperfecta
DPP - Dentin phosphoprotein
DSP - Dentin sialoprotein
DSPP - Dentin sialophosphoprotein gene
FPM - First permanent molars
IHS - Inhalation sedation
LL - Lower left
LR - Lower right
MDT - Multidisciplinary team
OVD - Occlusal vertical dimension
PEB - Post-eruptive breakdown
SSC - Stainless steel crown
UL - Upper left
UR - Upper right

Introduction

Dentinogenesis imperfecta (DI) is a rare genetic disorder characterised by abnormal dentine structure and curtailed mineralisation.[1] It can present in both the primary and permanent dentitions with a plethora of unique clinical and radiographic features. Approximately 1 in 45,000 of the general population are affected by DI, and it is slightly higher in the Black African population of South Africa.[2,3]

This autosomal dominant condition is linked to mutations in collagen type I matrix genes COL1A1 and/or COL1A2, usually classified as Type 1 DI and associated with the condition called osteogenesis imperfecta (prevalence 1 in 20,000). This disorder is also linked to the mutation of dentin sialophosphoprotein (DSPP) gene, which is responsible for expressing dentin sialoprotein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP) (non-collagenous proteins of dentine organic matrix which regulate mineralisation and hydroxyapatite formation).[3] A DSPP defect and subsequent deficient dentine

mineralisation is inherited in an autosomal dominant manner, has prevalence of 1 in 6000 to 1 in 8000 and is classified as Type 2 isolated DI.[3] Both Types 1 and 2 have very similar clinical and radiographic presentations.

Clinical presentation and associated anomalies

The affected dentition has amber/brown or grey/blue opalescent appearance (**Figure 1**) and is highly susceptible to enamel chipping due to the defective dentine-enamel junction (DEJ) bonds and rapid dentine attrition. Post-eruptive breakdown (PEB) and tooth-wear can further lead to pulpal exposures and the development of periapical pathologies, such as apical abscesses. This is most noticeable in primary teeth due to the large pulps. As a result, tooth surface loss is rapid, leading to reduction in occlusal vertical dimension.[2,4]

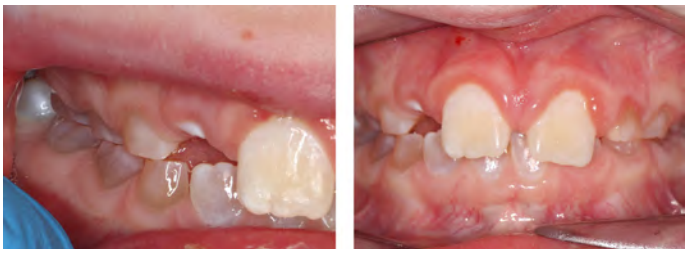

Figure 1. Tooth appearance in DI.

Depending on the classification and the severity of the condition, patients with DI can have a variety of radiographic manifestations. Crowns of the affected teeth can appear dysmorphologically bulbous with short and thin roots. In turn, the abnormal crown morphology of the second primary molar can lead to ectopic eruption and impaction of first permanent molars (FPM).[3,5,6]

Another significant characteristic of DI is tertiary dentine deposition and pulp chamber obliteration (**Figure 2**). According to the literature, this is associated with an increased attrition-related permeability of the enamel and dentine, which can then initiate pulp necrosis and occlusion of the chamber.[7,8]

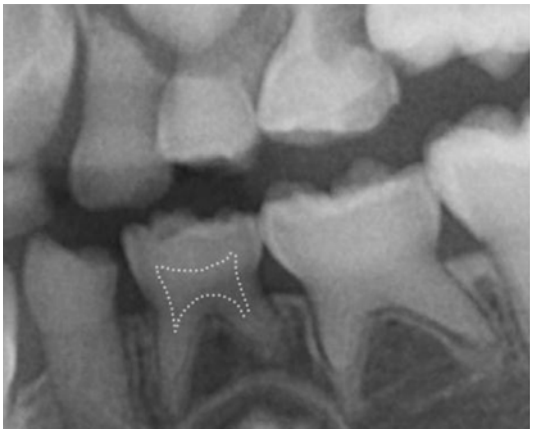

Figure 2. Section of a panoramic radiograph that shows a complete pulp obliteration in primary dentition.

Unlike amelogenesis imperfecta (a genetic disorder which presents with abnormal formation of the enamel), hypodontia (one to six teeth congenitally missing) is rarely associated with DI. Instead, there are several external influences that can damage the early dental tissues, the dental lamina, which are associated with missing teeth: infection, medications, chemotherapy, radiation therapy, dental trauma, endocrine abnormalities and intrauterine disturbances.[1,4]

This case report highlights the importance of a holistic approach to treating patients with hereditary enamel and dentinal defects, as the variety of clinical and systemic presentations and a substantial psychological factor present a myriad of implications and challenges for both the patient and the clinician.

Case

Written informed consent was obtained from the patient and the patient's parents. A 7-year-old boy presented to the University of Manchester Dental Hospital Department of Child Dental Health with his mother.

> *He was concerned about the aesthetics of his upper anterior teeth, in particular the translucent, yellow/brown appearance of the primary dentition and receding gingiva in the upper anterior region.*

Maternal history was significant for a diagnosis, as mother claimed that her teeth had a similar appearance and she has been diagnosed with DI Type 2. The patient's medical history included well-controlled asthma, mild allergic rhinitis and eczema. The mother denied the child having any previous sclera discolourations, bony fractures, bone pain or joint problems, which are all features of osteogenesis imperfecta, which is commonly linked to DI Type 1. The behaviour assessment showed a severe dental anxiety/phobia.

Extra-orally, the child had a normal stature and the sclera of his eyes were white. An intra-oral examination revealed an early mixed dentition which was clinically and radiographically caries-free. Oral hygiene was satisfactory. Bilateral partially erupted and ectopic upper first permanent molars were noted, with associated severe resorptive cavities distal to the upper right and left second primary molar teeth (URE and ULE). Primary teeth showed classic amber discolouration with signs of attrition (**Figure 3**). He also had a class 2 division 1 incisor relationship with an increased overbite.

Figure 3. Primary dentition with signs of attrition and PEB.

A DPT radiograph revealed that 6 permanent teeth (UR4, UR5, UL4, UL5, LL5 and LR5) were developmentally absent. The primary molars were small and bulbous with pulp canal obliteration and canal thinning. Roots were short and blunted. UR6/UL6 were ectopic with resorption of the distal aspects of URE/ULE (**Figure 4**).

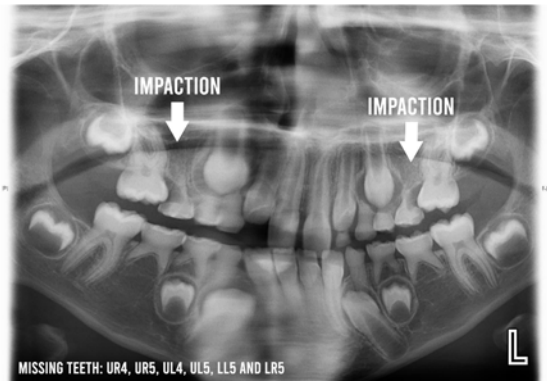

Figure 4. Panoramic radiograph of the case patient with DI.

As the patient had a normal stature, white sclera and no history of any joint issues or bony fractures, DI Type 1 related to osteogenesis imperfecta was disregarded.

Based on the patient's history, clinical and radiographic examination, the following diagnoses were made:
1. DI Type 2
2. Impacted upper first permanent molar teeth.
3. Hypodontia: developmentally absent UR5, UR4, UL4, UL5, LL5, LR5

All diagnoses were discussed with the patient and his mother. It was also explained that a further assessment with a multidisciplinary team (MDT) was necessary due to the complexities and rarity of these three anomalies being present simultaneously.

Due to the severe impaction of both upper FPMs, the patient underwent interceptive extractions of the URE and ULE to facilitate the eruption and mesial drifting of FPMs (**Figure 5**).[10,11] This treatment pathway was chosen as the second primary molars had a poor prognosis with severe unrestorable resorption. The procedure was carried out under inhalation sedation (IHS) due to high levels of dental anxiety. Six months post-extraction, the clinician will review the patient to assess the eruption of current permanent dentition and to consider restorative options for the missing teeth.

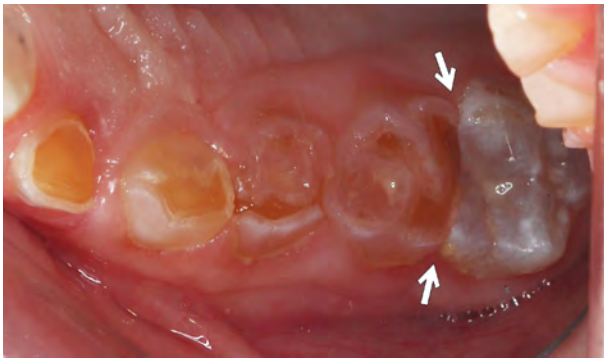

Figure 5. Impacted upper first ermanent molars.

Discussion

Management of patients with DI presents multiple challenges: both clinical aspects of care and the patient's psychological wellbeing need to be taken into account. Poor dental aesthetics and increased dentine sensitivity, as well as hypodontia and ectopic eruption, bring a plethora of challenges to both the patient and the practitioner.
Patients with similarly complex conditions are very likely to be affected by dental anxiety/phobia[1,12] as they require more frequent dental and hospital visits. Such situations call for the application of different behaviour management techniques: psychological (e.g. behaviour shaping) and pharmacological (e.g. IHS, intravenous sedation, general anaesthetic). The aim here is to successfully complete the treatment whilst avoiding a negative experience and fostering a positive relationship with the dental team.

> *The clinical concern when treating DI is to prevent tooth wear and dentine sensitivity by protecting the enamel through early placement of fissure sealant, stainless steel crowns (SSCs) or cuspal coverage restorations on both primary and permanent molars.*

In the described case the placement of SSCs on lower primary molars was avoided, as this would have likely hastened their exfoliation[13] and the aim was to maintain primary teeth for as long as possible due to lack of successors.

Affected anterior teeth can be restored functionally and aesthetically with direct and indirect composite/porcelain restorations. Further oral hygiene support is crucial in preventing pulpal bacterial ingress, pulpal necrosis and periapical abscesses.[1,4]

Impacted FPMs occur as the result of abnormal teeth eruption.[14,15] If impaction is left untreated, FPMs can erupt with malocclusion, such as mesial tipping and rotation.[1] Early treatment is imperative to correcting the path of eruption and preventing resorption of adjacent primary molars. Treatment options for impacted teeth include monitoring for spontaneous correction, placement of separator or active appliance and interceptive extraction of the second primary molar.[9-11,12-15] Early loss of URE and ULE was unfortunate due to the missing successor teeth; however, due to the extent of the resorption, both teeth had a hopeless prognosis and extraction was deemed the most appropriate option.

This case highlights the complexity of simultaneously managing three dental anomalies and emphasises the importance of seeking specialist advice from an interdisciplinary team in similarly intricate cases. In this particular case, the team would include consultants from Paediatric Dentistry, Restorative Dentistry and Oral Surgery. Restorative specialists could consider retaining and restoring primary molar teeth going into adulthood, in order to maintain the vertical dimension of affected dentition, as well as considering prosthetic replacement of the developmentally absent or prematurely lost teeth. Orthodontic and oral surgery specialists may consider more advanced restorative options for managing the spaces caused by hypodontia, for example, additional orthodontic extractions or crowns, bridges and dental implants once growth has completed.[4] As patients with DI are more likely to have molar-cross-bite and Class 3 malocclusions an orthodontic treatment should be well-planned due to the higher risks of root resorption.[16]

Conclusion

The presented case report describes a holistic and systematic approach to treating a unique patient with three dental anomalies: DI Type 2, impacted FPMs and hypodontia. Early clinical identification, close monitoring and long-term comprehensive MDT-integrated management of each anomaly is crucial for prevention of potential complications. Furthermore, this approach to treatment can improve the compromised aesthetics and function, thereby helping the overall mental and physical wellbeing of the patient, as the treatment plan is likely to be carried out throughout their entire life.

Acknowledgment Thanks to the young patients and their parents/guardians for allowing us to reproduce their clinical photographs.

Contribution statement All authors contributed equally to the work. All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work. All authors drafted the work or revised it critically for important intellectual content and gave final approval of the version to be included in Inspire

References

1. Duggal M, Cameron A, Toumba J (2012). Paediatric dentistry at a glance. 1st ed. Wiley-Blackwell, London.
2. Chetty M, Roberts T, Stephen L, et al. Hereditary dentine dysplasias: terminology in the context of osteogenesis imperfecta. British Dental Journal. 2016;221(11):727-730.
3. de La Dure-Molla M, Philippe Fournier B, Berdal A. Isolated dentinogenesis imperfecta and dentin dysplasia: revision of the classification. European Journal of Human Genetics. 2014;23(4):445-451.
4. Welbury R, Duggal M, Hosey M (2012). Paediatric dentistry. Oxford University Press. Oxford.
5. Biria M, Fatemeh, M A, Mozaffer S et al. Dentinogenesis imperfecta associated with osteogenesis imperfecta. Dent Res J 2012; 9: 489–494.
6. Barron M J, McDonnell S T, MacKie I et al. Hereditary dentine disorders: Dentinogenesis imperfecta and dentine dysplasia. Orphanet J Rare Dis 2008; 20: 31.
7. Malmgren B, Lundberg M, Lindskog S: Dentinogenesis imperfecta in a six-generation family. A clinical, radiographic and histologic comparison of two branches through three generations. Swed Dent J 1988; 12: 73–84.
8. Acevedo AC, Santos LJ, Paula LM, et al.: Phenotype characterization and DSPP mutational analysis of three Brazilian dentinogenesis imperfecta type II families. Cells Tissues Organs 2009; 189: 230–236.
9. Hafiz Z. Ectopic eruption of the maxillary first permanent molar: a review and case report. Journal of Dental Health, Oral Disorders & Therapy. 2018;9(2):154-158.
10. Hennessy J, Al-Awadhi E, Dwyer L, et al. Treatment of ectopic first permanent molar teeth. Dent Update. 2012;39(9):656–658.
11. Barberia-Leache E, Suarez-Clúa M, Saavedra-Ontiveros D. Ectopic eruption of the maxillary first permanent molar: characteristics and occurrence in growing children. Angle Orthod. 2005;75(4):610–615.
12. Grisolia B, dos Santos A, Dhyppolito I, et al. Prevalence of dental anxiety in children and adolescents globally: A systematic review with meta-analyses. International Journal of Paediatric Dentistry. 2021; 31: 168– 183.
13. Araujo MP, Hesse D, Bonifácio CC, et al. Hall Technique reveals faster exfoliation in primary molars compared to ART-2 years RCT. Eur Arch Paediatr Dent 2019; 20: 127-237.
14. Young D. Ectopic eruption of permanent first molar. J Dent Child. 1957;24:153–162.
15. Bjerklin K. Ectopic eruption of the maxillary first permanent molar. An epidemiological, familial, etiological and longitudinal clinical study. Swed Dent J. 1994;100:1–66.
16. Ravinet C, Garrec P. Orofacial rare diseases: specificities of the collaboration between orthodontist and pediatric dentist. Journal of Dentofacial Anomalies and Orthodontics. 2014;17(2):203.

Research Article

The anatomical success of treating rhegmatogenous retinal detachment with silicone oil compared to gas tamponade

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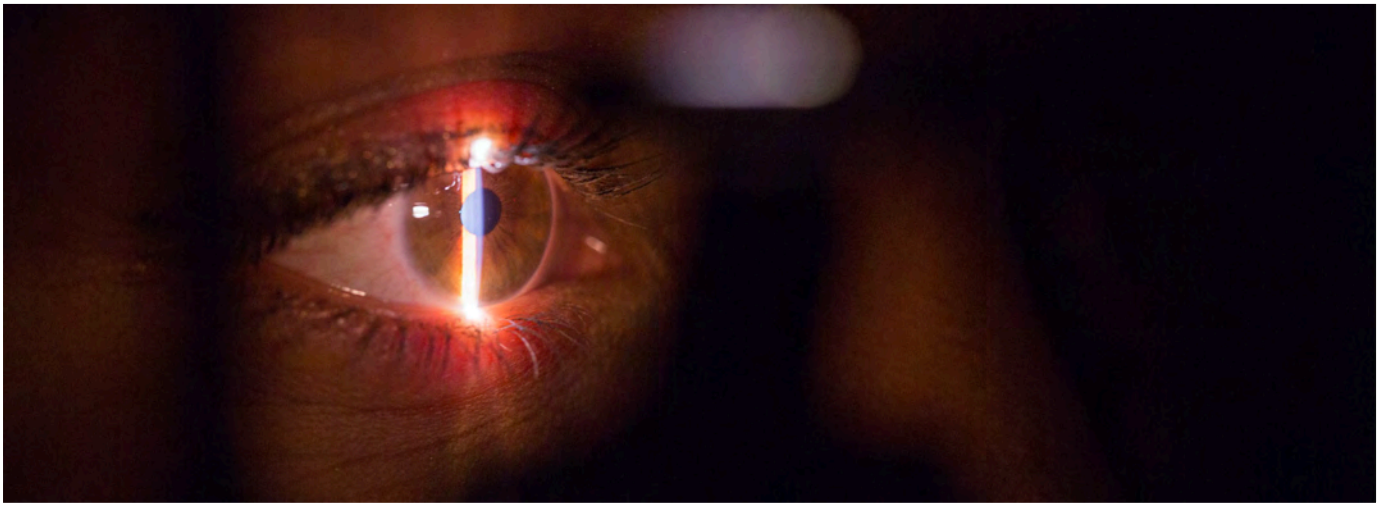

Abstract

Introduction Silicone oil and gas are used as internal tamponades via pars plana vitrectomy for the treatment of rhegmatogenous retinal detachment. The success of retinal reattachment is of primary interest as it forms the foundation for visual outcomes post-operatively. Thus, the aim of this paper is to determine which of these interventions most reliably leads to anatomical success.

Methods PubMed was the main database used to search the literature, in conjunction with Google Scholar. The results of the searches were further examined if they met the selection criteria for this review.

Results The method used yielded three RCTs and one retrospective cohort study. Three of these papers provided information that supported the use of gas tamponade; however, there was conflicting evidence within these studies. Although these investigations found that gas tamponade achieved greater rates of anatomical success, this was not statistically significant for complete retinal attachment or if the eye had not undergone previous vitrectomy. Another study also found that more surgeries had to be undertaken with gas tamponade compared with silicone oil before anatomical success was achieved.

Conclusion The results provided limited and conflicting evidence as to which tamponade would lead to greatest anatomical success. Recommendations would be to perform larger studies, using eyes with similar baseline characteristics before being randomised to either silicone oil or gas tamponade. Providing a long-term follow up of results would also provide greater insight into prolonged anatomical success between the two interventions.

Abbreviations

PPV - Pars plana vitrectomy
RCT - Randomised control trial
RD - Retinal detachment
RRD - Rhegmatogenous retinal detachment
SO - Silicone oil

Introduction

Retinal detachment (RD) is described as the "separation of the neurosensory retina from the underlying retinal pigment epithelium".[1] RD can be classified as either rhegmatogenous, tractional or exudative.[2] Tractional RD is caused by progressive contraction against the retina, most commonly due to proliferative diabetic retinopathy.[2] Exudative RD is rare; it is mostly caused by tumours of the choroid and occurs when subretinal fluid leaks due to the outer blood-retinal barrier becoming damaged.[2] In this paper, the focus is rhegmatogenous RD (RRD), in which intraocular fluid accumulates in the subretinal space due to a retinal break.[3]

> *RRD affects around 1 in 10,000 individuals annually, affecting mainly males as well as individuals with high myopia, or those who have experienced blunt trauma.*[3,4]

RRDs can be treated via pars plana vitrectomy (PPV) with the use of either silicone oil (SO) or gas tamponade.[5] This is achieved by making 1mm cuts in the sclera to gain access to the vitreous humour, which

is removed via suction.[6] The vitreous is then replaced with either a gas bubble (which naturally absorbs within two weeks) or SO, which is removed at a later date.[6]

When deciding upon the type of tamponade medium for RRD, anatomical success (defined as successful reattachment of the retina in the absence of an intraocular tamponade) is of primary interest, as this forms the foundation for visual outcomes post-treatment. Thus, the aim of this paper is to compare the anatomical success between SO and gas tamponade when treating RRD.

Method

A PubMed search was conducted using the search terms, "(Rhegmatogenous Retinal Detachment) AND (Silicone Oil) OR (Gas Tamponade) AND (Anatomical Success)". Eligibility of retrieved literature for analysis was determined through screening against pre-determined inclusion and exclusion criteria **(Table 1)**. The same search was conducted through the Cochrane Library, but no new relevant information was retrieved. Further information was collected via Google Scholar, using the same search terms to obtain general information with regards to RRD and its current treatment options. Searches were carried out in November 2019 to February 2020.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Comparison of SO and gas tamponade via PPV.	Any comparison to scleral buckle as a treatment.
Using eyes which had RRD.	Using eyes which had macula holes.
Using eyes which had RRD with no specific or exclusive pathological cause.	Using eyes which had RRD specifically and exclusively caused by pathological diseases, such as HIV and/or diabetes.
Results related to the anatomical success of using SO and gas tamponade via PPV.	Using eyes that had undergone recurrent RRD before the study was performed.
Papers published in English language.	Interventions that used a mixture of gas and oil as one tamponade.

Results

Initial searches retrieved 261 articles for analysis. After screening against the pre-determined eligibility criteria, only four studies were identified for qualitative analysis. The papers analysed consisted of three randomised control trials (RCTs)[7-9] and a retrospective cohort study **(Table 2)**.[10]

Three papers provided evidence which favoured the use of gas tamponade. In one of the RCTs,[9] complete retinal attachment was achieved in 73% of eyes using gas and 64% using oil, but the difference was not statistically significant. Despite this, the same study found that gas tamponade achieved better complete posterior retinal re-attachment with a success rate of 83% with gas versus 60% with oil (p=0.045).

Furthermore, in another RCT conducted by Abrams *et al.*,[8] it was also shown that, on eyes that had undergone previous vitrectomy, gas treatment had a significantly higher rate of complete retinal reattachment at 18-36 months (p<0.05). However, for eyes without previous vitrectomy, macular attachment was maintained in all eyes with no differences between SO- and gas-treated eyes.

In addition, the retrospective cohort study by Banerjee *et al.*[10] found that eventual anatomical success was 100% with gas (15 eyes treated) and 93.9% with SO (49 eyes treated). However, it should be noted that this finding was not statistically significant. In addition, four of the eyes treated with gas had to undergo repeat PPV with SO and one eye required repeat gas tamponade before anatomical success was achieved.

However, in the RCT by Hammer *et al.*,[7] the chance of successful reattachment was 50% greater with SO as opposed to gas, but this was not statistically significant. In this study, 18 eyes were treated with SO and 16 with gas tamponade.

Discussion

> *The results provided limited and conflicting evidence as to which tamponade medium is best to treat RRD.*

Although the RCT by Hammer *et al.*[7] suggested that SO was more successful, the small sample size used reduces the power of this study.
In addition, Banerjee *et al.*[10] demonstrated that more of the gas-treated eyes had to undergo repeat PPV, which arguably diminishes the marginal difference in eventual anatomical success between the two interventions. This difference may also be attributed to the fact that 14 of the eyes treated with SO had a more severe retinal tear of >180 degrees, whereas only one of the eyes treated with gas had this baseline characteristic. Furthermore, an additional 34 eyes were treated with SO. Given the larger sample size, the likelihood of achieving 100% eventual anatomical success is understandably reduced.

However, of interest was the study carried out by Abrams *et al.*,[8] which had a sample size of 265 eyes and an almost equal ratio of eyes treated with gas to SO tamponade (gas, n=121 eyes; SO, n=128 eyes).

> *The study findings suggested that gas was more successful at producing long-term retinal re-attachment.*

However, despite the large sample size and randomised design, the findings from one investigation alone cannot be relied upon. However, it can be argued that the remaining RCT[9] provides sufficient and reliable evidence that supports the use of gas tamponade, particularly in favour of posterior retinal reattachment. With this study being performed by the Silicon Study Group (a collaborative group of authors) these results are likely to be of great scientific robustness.

In conclusion, although the studies suggest that gas tamponade is better than SO in treating RRD, more data needs to be collected. The current cohort sizes are simply too small to make any direct links between experimental findings and the general population. It is also important to note that the studies[8,9] of greatest power, due to their large sample sizes and randomised design, were completed in the 1990s. It is possible that surgical techniques have progressed to provide improved outcomes, which could alter the results. Furthermore, as previously mentioned, SO seems to be used for more severe RRD, which could result in less successful outcomes for SO-treated eyes due to a worse baseline pre-intervention. Thus, future studies should aim to use larger cohort sizes with eyes of equal RRD severity to ensure that baseline characteristics are as similar as possible before randomisation to either gas or SO treatment. In addition, longer follow-up periods would allow monitoring of long-term differences in choice of tamponade medium.

It may also be of interest to evaluate how length of SO tamponade and SO removal affects eventual anatomical success. However, one would assume that the longer a tamponade is left in, the greater the chance of anatomical success. Thus, there may be significant ethical limitations surrounding short-term use of SO tamponade.

Table 2. Summary of included papers.

Author (date published)	Title	Study Design	Number of eyes tested	Summary of results
Silicon Study Group (1992)	Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Silicone Study Report 2	RCT	265	Gas tamponade was more likely to achieve retinal reattachment in comparison to SO, but this was not statistically significant. However, complete posterior retinal reattachment was more successful with the use of gas tamponade, which was statistically significant in comparison to SO.
Abrams *et al*. (1997)	Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. Silicone Study report 11	RCT	265	On eyes which had undergone previous vitrectomy, gas treated eyes had a higher rate of complete retinal reattachment, which was statistically significant. However, differences in macula attachment were not statistically significant in eyes which had no previous vitrectomy.
Banerjee *et al*. (2017)	Silicone oil versus gas tamponade for giant retinal tear-associated fovea-sparing retinal detachment: a comparison of outcome	Retrospective cohort study	64	Anatomical success was greater in gas treated eyes than SO, but this was not statistically significant. In addition, five gas treated eyes had to undergo one repeat surgery.
Hammer *et al*. (1997)	Complex retinal detachment treated with silicone oil or sulfur hexafluoride gas: a randomized clinical trial	RCT	34	Chance of successful retinal reattachment was 50% greater with SO tamponade as opposed to gas, but this was not statistically significant.

In addition, research into how different types of gas (e.g., sulphur hexafluoride, perfluoropropane or octofluropropane) affect anatomical success could be beneficial, as the studies included here used a range of different gases which may have contributed to differences in results.

Finally, all the studies examined here randomised more eyes to SO than gas tamponade, but the reasons for this were not addressed. Thus, it may be of interest to perform both a quantitative and qualitative study to determine the proportion of eyes treated with SO tamponade for RRD and factors influencing why SO was used by the surgeon. From this, further studies can be performed to justify or contradict surgical choices.

Contribution Statement The retrieval, screening, analysis and conclusions drawn from the studies selected were undertaken by the author. This article has undergone several revisions via the peer review and copy-editing process, and the final draft has been approved for inclusion in Inspire.

References

1. Kang HK, Luff AJ. Management of retinal detachment: a guide for non-ophthalmologists. BMJ (Clinical research ed), 2008; 336(7655):1235-40.
2. Khalil M, Kouli O. The Duke Elder Exam of ophthalmology: a comprehensive guide for success. CRC Press; 2020. p. 227.
3. Veith M, Stranak Z, Pencak M, et al. 25-gauge vitrectomy and gas for the management of rhegmatogenous retinal detachment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2019;163(1):80-4.
4. Ghosh YK, Banerjee S, Savant V, et al. Surgical treatment and outcome of patients with giant retinal tears. Eye (Lond). 2004;18(10):996-1000.
5. Lin T, Mieler WF. Management of Primary Rhegmatogenous RD: Review of Ophthalmology; 2008 [Available from: www.reviewofophthalmology.com/article/management-of-primary-rhegmatogenous-rd. Accessed: 26 February 2020.
6. Turner R. Vitrectomy. Information for patients.: Oxford Radcliffe Hospitals NHS Trust; 2009. p. 8.
7. Hammer M, Margo CE, Grizzard WS. Complex retinal detachment treated with silicone oil or sulfur hexafluoride gas: a randomized clinical trial. Ophthalmic Surg Lasers. 1997;28(11):926-31.
8. Abrams GW, Azen SP, McCuen BW, et al. Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. Silicone Study report 11. Arch Ophthalmol. 1997;115(3):335-44.
9. Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Silicone Study Report 2. Arch Ophthalmol. 1992;110(6):780-92.
10. Banerjee PJ, Chandra A, Petrou P, Charteris DG. Silicone oil versus gas tamponade for giant retinal tear-associated fovea-sparing retinal detachment: a comparison of outcome. Eye (London, England). 2017;31(9):1302-7.

Research

Targeting glioma stem cells with Zika virus

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive type of brain tumour and is widely regarded as incurable. The low therapeutic outcomes of GBM may be associated with glioma stem cells (GSCs) that reside in the tumour and demonstrate stem-like, self-renewing and tumourigenic capabilities. Research into Zika virus (ZIKV) has shown that it displays an oncolytic activity against GSCs. This report will explore the way that ZIKV invades and induces apoptosis in GSCs and its potential for therapeutic application.

Abbreviations

AXL - Anexelekto
GBM - Glioblastoma multiforme
GSC - Glioma stem cells
IFN-1 - Type 1 interferon
IRF - IFN-regulatory factor
ISG - IFN-stimulated gene
MAV - Mitochondrial antiviral-signalling protein
NF-κB - Necrosis factor κB
NPC - Neural progenitor cell
OV - Oncolytic viral
PAMP - Pathogen-associated molecular pattern
PRR - Pattern-recognition receptor
RIG - Retinoic acid-inducible gene
STAT - Signal transducer and activator of transcription
TMZ – Temozolomide
WT ZIKV - Wild type Zika virus
ZIKV - Zika virus

Introduction

GBM is a potentially lethal form of primary brain tumour that starts in neural progenitor cells (NPCs).[1] Around 2,200 cases of GBM are diagnosed in England each year, accounting for 55% of all malignant brain tumours.[2] Despite maximal therapy with surgery, radiation, and chemotherapy, the recurrence rate for GBM remains high and median survival from the point of diagnosis is only 14 months.[2] This may be attributable to GSCs, which have been shown in preclinical models to resist all forms of conventional cancer therapy.[3] Therefore, strategies to target these cells specifically may possibly improve patient response to treatment regimes. Oncolytic viral (OV) treatment with ZIKV might be a potential way to achieve this via stimulation of the intrinsic and extrinsic apoptotic signalling cascades.[4] This potentially devastating virus is known to target NPCs in the foetus and cause microcephaly.[5] However, adults infected with the virus typically develop only mild symptoms and the therapeutic application of an attenuated ZIKV strain has been indicated to further reduce the pathological response.[6,7] Therefore, the aim of this review is to explore the role and mechanism of ZIKV for targeting GSCs in cases of GBM and how patient safety is maintained with the use of the attenuated ZIKV strain.

Literature search

A literature search was conducted using the NCBI platform (PubMed Central) for the term "Glial Stem Cells" and 52,861 results were retrieved. To obtain the latest scientific data, the publication date was restricted to 2015-2020 and the results were narrowed down to 32,082 articles. Titles and abstracts of retrieved literature were screened for relevance against pre-determined inclusion criteria. Papers were eligible for inclusion if they explored the role of glial stem cells in GBM recurrence. A search in the same database for the term "Zika in glioblastoma" retrieved 535 results. Articles were retained only if they explained the effect of ZIKV on GSCs. Furthermore, the National Cancer Registration and Analysis website was reviewed to obtain valid and reliable values for the incidence and survival rate of GBM patients in the UK. This evidence was obtained from data linkage between the National Cancer Registration Service and the Radiotherapy Data Service.

Mechanisms of ZIKV internalisation

ZIKV penetrates host cells via receptor mediated endocytosis.[8] Evidence from human glioblastoma specimens has shown that anexelekto (AXL) tyrosine kinase receptors and their ligand, growth arrest-specific 6 (Gas6), play an essential role in this mechanism.[8] Gas6 acts as a co-factor by binding to ZIKV and allowing attachment of the virus to the AXL receptors on GSCs. Once the ZIKV-Gas6 complex activates the receptor, the virus can enter the cell via clathrin-mediated endocytosis.[8] Clathrin proteins coat the pits formed on the inner surface of the plasma membrane during endocytosis of ZIKV. These pits form vesicles that allow transport of the virus into the cytoplasm.[9] Noteworthily, both AXL and Gas6 have been found to be overexpressed in GSCs supporting ZIKV specificity to these cells.[10] However, conflicting evidence has indicated that the virus is able to infect modified GSCs that are deprived of the AXL receptor.[11] Thus, the exact mechanism of ZIKV internalisation is still unclear.

The role of ZIKV in the induction of the extrinsic apoptotic pathway in GSCs

The first line of defence against invasive pathogens is exerted by the innate immune system, which is central in the extrinsic apoptotic signalling cascade.

> *This cascade is comprised of pattern-recognition receptors (PRRs) that demonstrate a pivotal role in the detection of pathogen-associated molecular patterns (PAMPs).*[12]

In the case of ZIKV infection, retinoic acid-inducible gene (RIG)-like receptors serve as PRRs and activate the mitochondrial antiviral-signalling proteins (MAVs). These proteins induce necrosis factor κB (NF-κB) and IFN-regulatory factor (IRFs), which activate the transcription of type 1 interferon (IFN-1) genes and facilitate IFN-α/β production. Once IFN-α/β are produced, they are secreted from the infected cells into the extracellular space, where they bind to IFN-α/β receptor that may be found on either the same cell or on uninfected cells in the surrounding area. Following the stimulation of this receptor, a second transcriptional cascade is induced by signal transducer and activator of transcription (STAT) 1 and 2 factors that lead to the overexpression of IFN-stimulated genes (ISGs), which are involved in cellular apoptosis.[13,14]

Nevertheless, it has been shown that ZIKV exhibits an inhibitory effect on IFN-1 induction and signalling cascades via the NS5 viral protein (**Figure 1**).[14] Overall, ZIKV acts to suppress the induction of IFN-1 by downregulating NF-κB- and IRF-induced signalling. In addition, ZIKV impedes the activating phosphorylation of both STAT1 and 2, and drives the proteasomal degradation of STAT2, thereby inhibiting IFN-1 signalling.[13,14] This information inspired scientific efforts to introduce mutations in the NS5 gene of ZIKV with the aim of attenuating the virus and making it more susceptible to the IFN-1 innate immune response.[7]

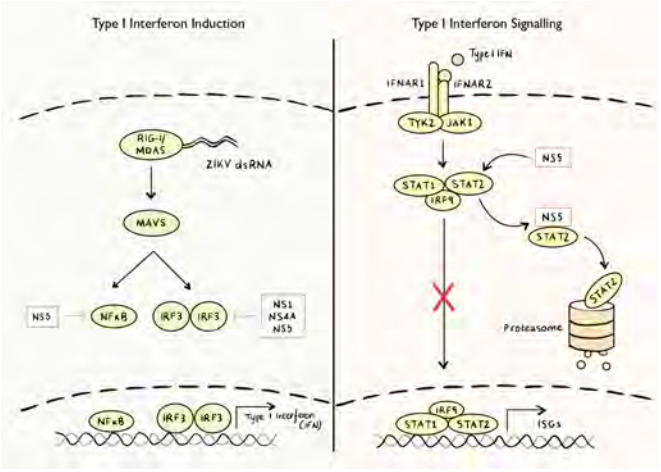


Figure 1. The impact of NS5 viral proteins on IFN signalling. NS5 viral proteins inhibit NF-κB and IRFs, interfering with the induction of IFN-1. In addition, they interact with STAT-2, inducing the proteasomal degradation of this protein and constraining IFN-1 signalling. Figure from Kumar et al;[13'] adapted with permission.

Genetically modified ZIKV strains in OV treatment of GBM

In order to optimise the safety of ZIKV for therapeutic application in GBM patients, the ZIKV viral genome has been altered. The modified ZIKV strain contains two nucleotide changes in the same codon of the NS5 gene. Therefore, the likelihood of regression back to the pathogenic viral form is low as two simultaneous nucleotide changes are required.[7] Moreover, the effect of this modified strain on GSCs can be enhanced with concurrent temozolomide (TMZ) chemotherapy as the virus downregulates expression of ABC transporters. These transporters are cell-membrane proteins that act as molecular pumps in GSCs to expel cytotoxic drugs from the cytosol.[15] Therefore, ZIKV increases the vulnerability of GSCs to chemotherapeutic agents.

A study performed in-vivo on mouse glioma models and in-vitro on glioblastoma tissues obtained from patients compared the tumouricidal effects of the wild type ZIKV (WT-ZIKV) form and its recombinant derivative E218A with NS5 mutations. Both the WT-ZIKV and the E218A strain displayed oncolytic activity against GSCs. However, the WT-ZIKV strain was much more effective than the mutated form in reducing GSC growth. Therefore, ZIKV E218A was tested in combination with TMZ chemotherapy to improve its potency. Although, TMZ alone had a limited effect on GSC growth, the combined treatment showed a great antitumor effect similar to that of the WT-ZIKV strain.[7] This study should be repeated in-vivo with GBM patients to explore whether the results are reproducible in humans and to determine any possible implications arising from the treatment.

Conclusion

Synthesis of the aforementioned evidence suggests that genetically engineered ZIKV strains may be utilised to target GSCs via OV therapy. The reason for viral tropism towards these specific cells remains unclear as no definitive ZIKV receptor has been found on them. The mechanism through which ZIKV delays the extrinsic apoptotic signalling pathway, improves its replicative capacity and pathogenicity. Fortunately, a genetically modified strain has been formulated to be more vulnerable, especially to the IFN-1 signalling mechanism, making it safer for use in treatment. This, in combination with chemotherapy, has shown great oncolytic effect in vitro. Nevertheless, human trials are fundamental to determine the safety and efficacy of this treatment in vivo. If the same effect is obtained, the survival rate of GBM patients may increase significantly and this will be a breakthrough, especially in this nascent area of cancer treatment.

Acknowledgements This article is based on a completed student selected component module as part of the Peninsula Medical School, University of Plymouth curriculum. Many thanks to Dr Claudia Barros (Associate Professor of Neuroscience; University of Plymouth, Plymouth, UK) who supervised this project.

Contribution statement The author made significant contributions to the conception of this work, analysis and interpretation of data, drafting and revising its intellectual content and approving the final version to be included in Inspire.

References

1. Stoyanov GS, Dzhenkov D, Ghenev P, Iliev B, Enchev Y, Tonchev A B. Cell biology of glioblastoma multiforme: from basic science to diagnosis and treatment. Med Oncol, 2018; 35(3): 27.
2. Greenberg D, Winters T, Brodbelt A, et al. Incidence and outcomes for cerebral Glioblastoma in England. Public health England, 2017.
3. Prager B C, Bhargava S, Mahadev V, et al. Glioblastoma Stem Cells: Driving Resilience through Chaos. Trends Cancer, 2020; 6(3): 223-235.
4. Su KY, Balasubramaniam VRMT. Zika Virus as Oncolytic Therapy for Brain Cancer: Myth or Reality?. Front Microbiol, 2019; 10: 2715.
5. Mlakar J, Korva M, Tul N, et al. Zika Virus Associated with Microcephaly. N Engl J Med ,2016; 374(10): 951-8.
6. Souza OIN, Barros-Aragao FGQ, Frost PS, et al. Late Neurological Consequences of Zika Virus Infection: Risk Factors and Pharmaceutical Approaches. Pharmaceuticals, 2019; 12(2): 60.
7. Zhu Z, Gorman JM, McKenzie LD, et al. Zika virus has oncolytic activity against glioblastoma stem cells. J Exp Med, 2017; 214(10).
8. Meertens L, Labeau A, Dejarnac O, et al. Axl Mediates ZIKA Virus Entry in Human Glial Cells and Modulates Innate Immune Responses. Cell Rep, 2017; 18(2): 324-333.
9. Kaksonen M, Roux A. Mechanisms of clathrin-mediated endocytosis. Nat Rev Mol Cell Biol, 2018; 19: 313-326.
10. Wu G, Ma Z, Cheng Y, et al. Targeting Gas6/TAM in cancer cells and tumor microenvironment. Molecular Cancer, 2018; 20.
11. Wells MF, Salick MR, Wiskow O, et al. Genetic Ablation of AXL Does Not Protect Human Neural Progenitor Cells and Cerebral Organoids from Zika Virus infection. Cell Stem Cell, 2016; 19(6): 703-708.
12. Serman TM, Gack MU. Evasion of Innate and Intrinsic Antiviral Pathways by the Zika Virus. Viruses, 2019; 11(10): 970.
13. Kumar A, Hou S, Airo AM, et al. Zika virus inhibits type-I interferon production and downstream signaling. EMBO rep, 2016; 17(12): 1766-1775.
14. Elshahawi H, Hassan SS, Balasubramaniam V. Importance of Zika Virus NS5 Protein for Viral Replication. Pathogens, 2019; 8(4):169
15. Lee CAA, Banerjee P, Wilson BJ, et al. Targeting the ABC transporter ABCB5 sensitizes glioblastoma to temozolomide-induced apoptosis through a cell-cycle checkpoint regulation. H Biol Chem, 2020; 295(22): 7774-7788.

Senior Editors, Autumn 2021

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

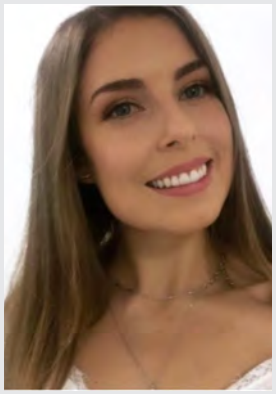
I joined the INSPIRE team last year as I really wanted to learn more about the publication process. Since completing my intercalated degree, I have become really interested in completing more research and becoming an INSPIRE Editor seemed like a great way to experience a different side to the research 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

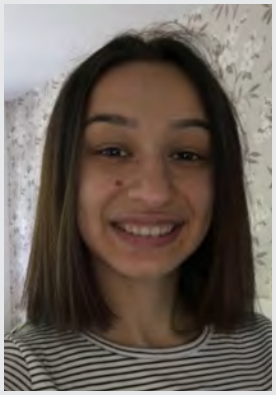
Hi, I'm Seanain and I'm a third year postgraduate dental student at Plymouth University. My journey with INSPIRE started during my undergraduate degree when I undertook a research studentship to develop a chair-side biomarker test for periodontal disease. I have really enjoyed being an editor for the 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

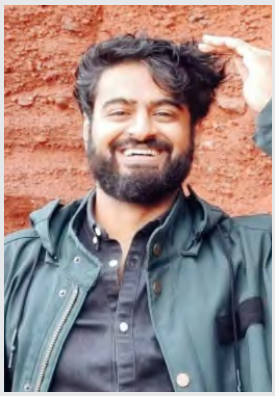


Cardiff University

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, Autumn 2021

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.

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University of Bristol

www.bristol.ac.uk/medical-school/study/undergraduate/inspire
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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

www.plymouth.ac.uk/about-us/university-structure/faculties/health/inspire

Leads: David Parkinson, Professor of Neuroscience;
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