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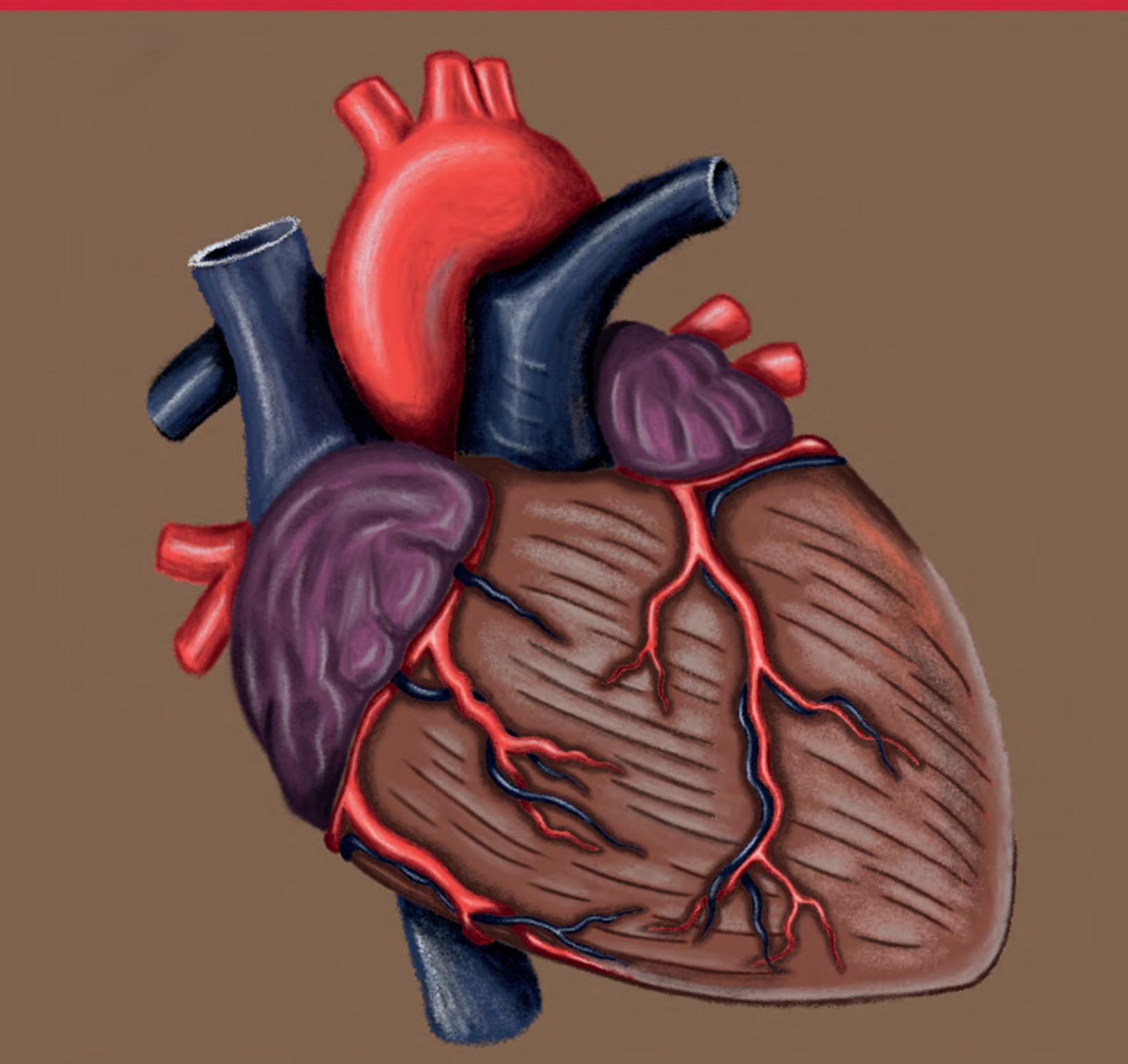

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Hi! Welcome to the Winter 2024/2025 issue of the INSPIRE Student Health Sciences Research Journal.

This issue has been written and peer-reviewed by students, with the editorial board being made up of students from the universities of Bristol, Cardiff, Exeter and Plymouth, the journal's founding institutes. The journal was created as part of the INSPIRE scheme, which aims to provide students in medical dental and veterinary schools across the UK with the opportunity to participate in research and encourage them to incorporate it into their future careers.

We hope you enjoy reading the INSPIRE Student Health Sciences Research Journal – the articles have been written and peer-reviewed by students throughout 2024. See all our past issues at **www.inspirestudentjournal.co.uk**. Find out more news, events, case studies and opportunities related to the INSPIRE programme at **gw4inspire.co.uk**.

Best wishes,

INSPIRE Student Health Sciences Research Journal Senior Editors

Front Cover

Cover image
by **Alvin Leung**

"The cover art was adapted from a piece that I have created two years ago, titled 'unlocking a heart'. The original piece featured a digitally hand-drawn human heart coupled with a short allegory composed of dialogues, exploring the elements of history-taking and the importance of connecting with patients on a deeper level to understand the patient perspective and narrative."

PLAGIARISM

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News & Opinion

Raising the red flag: w y captive primates experience welfare problems in zoos

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"Two chimps in a concrete enclosure with a rope and tyre, but nothing else. One chimp was huddled against a wall not moving, the other sat by the dirty glass window, staring out".[1] This is just one of the Red Flag Reports submitted to Born Free, a charity aiming to prevent the exploitation and suffering of captive wild animals. The charity created the "Raise the Red Flag" reporting system, allowing members of the public to report abnormal behaviour, poor husbandry and poor handling practices observed in captive-kept wildlife. From 2019 to 2024, Born Free has received over 17,000 reports, which are used to further investigate the welfare of zoo animals.[2]

Primates are the focus of many of these reports, with behaviours such as repetitive neck-twisting, over-grooming, vomiting and regurgitation having been reported.[1] These abnormal behaviours can represent poor welfare and are linked to housing primates in unsuitable environments.[3] Other poor welfare indicators include physiological abnormalities such as infertility and an increased incidence of veterinary problems compared to wild primates.[4,5]

The development of welfare problems appears to be more common in certain primate species compared to others.[5] The gentle lemur commonly exhibits welfare problems such as over-grooming and high morbidity, whereas the ring-tailed lemur appears to develop minimal behavioural and veterinary problems in captivity.[5] This leads us to question, why do primates develop welfare problems in captivity, and why are certain species more susceptible to developing problems than others?

The behavioural biology behind welfare problems in captivity

Non-human primates inhabit a large range of ecosystems throughout South America, Africa and Asia.[6,7] Within the wild, primates may inhabit large home ranges, form complex social groups and forage for many hours a day.[6,7] It is impossible to emulate the natural habitats of wild primates within captivity. Not only are captive habitats vastly smaller, but there is a continuous presence of keepers, veterinarians and visitors.[8] Primates have not evolved to live within these captive environments; due to the constraints of these exhibits, captive primates may not be able to exhibit commonly expressed behaviours by their wild counterparts.[9,10] This may induce stress within captive animals. Stress is a state of physiological and behavioural adjustment which occurs to maintain homeostasis (a self-regulating process to maintain internal stability) when environmental conditions are suboptimal.[10] If the animal continues to experience high levels of stress, biological processes may be negatively impacted, decreasing growth rates, suppressing the immune system and causing infertility.[10]

Additionally, this inability to exhibit natural behaviours may negatively impact the affective state (or 'feelings') of the animal, leading to the development of abnormal behaviours such as stereotypies.[9] Stereotypies are thought to originate from the chronic inability to exhibit behaviour in response to internal or external stimuli despite high motivation. Many of these behaviours are controlled by negative feedback loops, meaning the animal will stay within a high motivation state until the behaviour is performed.[9,10] Hence, the inability to perform these behaviours leads to stress and a state of chronic frustration (an emotion arising from the nonfulfillment of a desired goal).[11] Carrying out stereotypic behaviours releases dopamine which may help to reduce the chronic frustration and stress the animal is experiencing.[10] Thus, stereotypic behaviour may aid the animal in coping with their captive environment.

Although some stereotypic behaviours occur in the absence of poor welfare and function as 'self-enrichment',[3,10] many stereotypic

behaviours can become harmful to the animal and lead to poor welfare states.[8] For example, gorillas live in large social groups and naturally exhibit social grooming behaviour. When they are kept alone or in small groups, they may over-groom or self-mutilate as they are unable to carry out social grooming despite experiencing a high motivation to do so. This may cause the gorilla to redirect this motivation through hair pulling[9]. This can lead to injuries and negatively impact the health of the gorilla. Hence, the development of harmful stereotypies negatively impacts welfare.[8,9,10]

Why are some species more prone to welfare problems than others?

The motivation of primate species to exhibit species-specific behaviours is a product of natural selection and evolution within their ecological niche.[5,9] As different primate species have evolved in different environments, they will have varying levels of motivation to perform specific behaviours. For this reason, the inability to perform a specific behaviour will greatly impact species which have a high motivation but marginally impact the welfare of species with a low motivation to exhibit this behaviour.[5,9] Hence, some species are more suitable to living within captivity than others.

A study carried out by Pomerantz et al showed that primates that had access to larger home ranges in the wild exhibited a higher rate of pacing in captivity compared to species with smaller home ranges.[9] The red-faced spider monkey inhabits a home range of roughly 206 hectares, with a rough day journey range of 2400m.[9] Within captivity, they are kept in considerably smaller spaces. Due to the inability to carry out long day journeys within captivity, spider monkeys may redirect this motivation and begin to pace.[9] In contrast, the common brown lemur live in smaller home ranges of roughly 48.6 hectares, carrying out day journeys of 550m.[9] The motivation to carry out long day journeys is therefore lower and pacing behaviour is generally not exhibited within this species when kept in captivity.[9] Hence, an animal's natural biological behaviour greatly impacts their pre-disposition to welfare problems and ability to successfully live in captivity.

Conclusion

Many primate species face welfare problems in captivity, with certain species experiencing greater welfare issues than others. With the inability for certain behaviours to be exhibited in captivity, species with a high motivation to carry out these behaviours may be the most affected and subsequently develop abnormal behaviours. Thus, this raises the question of whether these species, which are predisposed to welfare problems, should be kept in captivity. As veterinarians, conservationists and members of the public, we have a duty to monitor the welfare of these species and 'raise the red flag' to prevent the suffering of captive primates.

References

1. Primate problems [Internet]. Born Free. [cited 2024 Feb 29]. Available from: https://www.bornfree.org.uk/raise-the-red-flag/primate-problems/
2. Raise the flag for captive wild animals [Internet]. Born Free. [cited 2024 Feb 29]. Available from: https://www.bornfree.org.uk/raise-the-red-flag/
3. Lutz CK, Coleman K, Hopper LM, Novak MA, Perlman JE, Pomerantz O. Nonhuman primate abnormal behavior: Etiology, assessment, and treatment. American Journal of Primatology. 2022 Apr 5;84(6).
4. Marchant-Forde JN. The science of animal behavior and welfare: challenges, opportunities, and global perspective. Frontiers in Veterinary Science. 2015 May 28;2.
5. Clubb R, Mason G. Pacing polar bears and stoical sheep: testing ecological and evolutionary hypotheses about animal welfare. Animal Welfare. 2004 Feb;13(S1):S33–40.
6. Galán-Acedo C, Arroyo-Rodríguez V, Andresen E, Arasa-Gisbert R. Ecological traits of the world's primates. Scientific Data [Internet]. 2019 May 13 [cited 2021 May 13];6(1):55. Available from: https://www.nature.com/articles/s41597-019-0059-9
7. Owen-Smith N, editor. Evolutionary transitions: from primate ancestors to modern humans [Internet]. Cambridge University Press. Cambridge: Cambridge University Press; 2021. p. 247–343. Available from: https://www.cambridge.org/core/books/abs/only-in-africa/evolutionary-transitions-from-primate-ancestors-to-modern-humans/C97D51E1BBF304666CB90E4C24061601
8. Learmonth MJ. Dilemmas for natural living concepts of zoo animal welfare. Animals [Internet]. 2019 Jun 5;9(6):318. Available from: https://www.mdpi.com/2076-2615/9/6/318
9. Pomerantz O, Meiri S, Terkel J. Socio-ecological factors correlate with levels of stereotypic behavior in zoo-housed primates. Behavioural Processes. 2013 Sep;98:85–91.
10. Wolfensohn S, Shotton J, Bowley H, Davies S, Thompson S, Justice W. Assessment of welfare in zoo animals: towards optimum quality of life. Animals [Internet]. 2018 Jul 4;8(7):110. Available from: https://www.mdpi.com/2076-2615/8/7/110
11. Bierzynska M, Bielecki M, Marchewka A, Debowska W, Duszyk A, Zajkowski W, et al. Effect of frustration on brain activation pattern in subjects with different temperament. Frontiers in Psychology [Internet]. 2016 Jan 11;6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4708012/

Phoebe Sussmann

Phoebe is a fourth-year veterinary student at the University of Bristol. She has a strong interest in zoological medicine, conservation and One Health. Last year, she completed an intercalated masters in Global Wildlife Health and Conservation at the University of Bristol, where she worked alongside the Cheetah Conservation Fund to evaluate the impact of wild carnivores on rabies transmission in Namibia. Outside of the degree, she has acted as an associate editor and advisor for the INSPIRE Journal from 2023 to 2024 and the editor for the Journal of the Association of Veterinary Students (JAVS) from 2022 to 2024. In her spare time, she enjoys hiking with her dogs and horse riding.

Review

Exploring artificial i telligence in dentistry

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Abstract

As the influence of artificial intelligence (AI) expands across digital landscapes, its integration into dentistry has become an increasingly important topic of discussion. Dental professionals and students alike may question how AI will shape the future of dental practice. This report examines the multifaceted role of AI within the dental field, focusing on its potential to enhance diagnostic accuracy, streamline treatment planning, enhance dental education and optimise patient management. Despite its advantages, the employment of AI in dentistry is not without challenges; ethical concerns regarding data protection and patient privacy are reviewed to underscore the importance of responsible AI use. By providing a detailed analysis of these aspects, this paper aims to offer a clear understanding of how AI is set to transform dental practices and education while addressing ethical considerations such as patient privacy and data security.

Abbreviations

AI - Artificial intelligence
CBCT – Cone Beam Computed Tomography
GDC – General Dental Council
GDPR – General data protection regulations
RCT – Root canal treatment
VR – Virtual reality

What is AI?

"Artificial intelligence is the new electricity."

Andrew Ng, the co-founder and former head of Google Brain, encapsulates the potential of AI in this single sentence.[1] AI marks the beginning of a new world, a transformative entity across countless domains; in the past 10 years alone, the number of AI companies in the UK has increased by a factor of six hundred.[2] Moreover, the recent launch of OpenAI's Chat GPT highlights the increasing prevalence of AI amongst the general population.

Artificial intelligence is the ability of computer programmes to carry out tasks that would typically require human intelligence. By using technology like machine learning, natural language processing and adaptive learning systems, AI can perform tasks like logical reasoning, problem-solving and learning.[3]

Current applications and benefits of AI in dentistry

Diagnostic tools

Dental radiographs (X-rays) are the primary source of diagnostic information in dentistry, with roughly 22 million taken annually in the UK.[4] Radiographs enable dental clinicians to identify different anatomical and pathological structures that are not readily visible on clinical examination.[5] The Faculty of General Dental Practice (UK) sets guidelines to ensure the standard of dental radiographs and ensure 'delivery of an accurate diagnosis'.[6] Albeit effective and widely relied upon, dental radiographs can be limited by subjectivity and misinterpretation despite quality assuring legislation from Public Health England[6] in line with Ionising Radiations Regulations 2017. This is corroborated by a study highlighting that one third of dental panoramic x-rays across 41 practices were deemed as 'unacceptable' quality.[7] Fatigue and human error are amongst reasons why there may be minor discrepancies between clinicians regarding missed or inaccurate diagnoses.

AI technologies offer a solution to this: by using its extensive patient database including case studies, AI can assess radiographs to

provide a more precise and accurate diagnosis to supplement the clinician's judgment.[8] In many cases, this technology has been shown to identify early-stage caries (the most prevalent dental disease, causing demineralisation of dental hard tissue), assess the extent of periodontal diseases, and even highlight potential cancers. AI can present this information in a clear, visual manner to highlight areas of concerns which clinicians can subsequently use to explain any diagnoses or treatments further without disengaging the patient.

Treatment planning: implant placement

Cone Beam Computed Tomography (CBCT) is a type of dental radiograph that is widely used for implant procedures. The process involves a rotational scan to produce 3D images of an individual's jaw and teeth; this radiograph can then be used to determine several things when planning an implant placement.[9] For example, identification of the maxillary sinuses can help determine whether a sinus lift is needed or if extra caution should be taken to prevent perforation. Similarly, a CBCT scan may be used to highlight the density and height of alveolar bone which will aid in correct implant sizing, and by determining the location of the mental foramen, treatment can be planned to reduce the risk of inferior alveolar nerve damage.

This is where AI can come into play. AI can explore these images in further detail, corroborating anatomical structures and making them easier to identify. AI can even produce virtual treatment plans and simulate surgical placements. These advancements can assist clinicians to ensure precise and optimal implant placements, focusing on critical details like the placement angle.[10] Thus, integration of AI not only improves diagnostic accuracy, but also plays a supporting role in strategic treatment planning.

Treatment planning: endodontics

Endodontics is a dental speciality that involves the pulp and tissues surrounding the roots of a tooth. The most common procedure in this field is known as root canal treatment (RCT) whereby infected pulp tissue is removed, and root canals are obturated with filling material like Gutta Percha.[11] One of the challenges that dentists face when carrying out this procedure is accessing the root canal system.[10] Genetic variation within patients may present as complex and irregular root canal systems; this may make the canals harder to access and increase susceptibility of re-infection post treatment.[11] Similarly, factors such as trauma and ageing may lead to intracanal hard tissue formations like pulp stones and tertiary dentine.[12] As a result, treatment may be complicated, often requiring extensive debridement and the use of specialist instruments.

AI-based software can be utilised to automate root canal detection by analysing radiographs; this helps dentists to locate complicated canal systems more precisely and efficiently.[13] Furthermore, AI can consider anatomical structures and irregularities, enabling dentists to enhance their treatment plans by recommending specific instrumentation techniques. For example, this includes optimising the types of rotary files to use to appropriately shape and irrigate irregularly shaped canals.[10] AI even encourages patient transparency by providing tailored success rates so that patients can make well-informed decisions about their care.[13]

AI in patient and practice management

Outside of treatment planning, AI can improve administrative tasks that are essential for the smooth operation of a dental practice. Over 18 million adults and 6 million children were seen by an NHS dentist over the past two years.[14] The demand for dental appointments is high and the lingering repercussions of COVID-19 continue to affect clinical capacity and patient access.

To be able to manage logistics and administration effectively, AI algorithms can schedule dental appointments individually tailored to the availability and preferences all of parties. It does this through analysis of extensive patient databases and practice data through natural language processing tools, which is the mode that allows digital devices to recognise, understand and generate text and speech.[10] Additionally, AI can send out automated appointment reminders to patients to encourage and increase attendance rates. A literature review examined the success of AI-generated text reminders across healthcare practices, showing 86% of studies reported a decrease in missed appointments as a result.[15] Dental practices can also manage their time more effectively and reduce waste by using AI to undertake tedious tasks like stocktakes and ordering.[10]

AI in dental education

The dental field is pioneering with the use of AI through virtual reality (VR) to enhance dental education.[16] By wearing a VR headset, students can immerse themselves in a range of clinical scenarios, from patient history taking to observing oral and maxillofacial surgery. Studies have shown that this teaching method can help students build confidence and fine tune interpersonal skills like empathy and communication to implement in real life situations. VR-based teaching has enabled more efficient tooth preparations for restorative fillings and crowns and an improved quality of implant placements, highlighted by an extensive systematic review.[17] This learning style is most effective when integrated with traditional dental teaching methods and has the scope to promote a safe learning environment to protect patients in the long term.

AI can also be advantageous to dental students when used as a personalised tutoring platform.[10] Advancements in AI technologies means that it is indiscriminate of ability, preferences, and individual needs; AI is accessible to anyone who wants to enhance their learning.[18] Students can compile copious amounts of learning material and suggested reading lists to streamline their studies simply by inputting data and specific prompts. Reflective practice is also encouraged as AI can produce personalised feedback and highlight areas of improvement for dental students to take on board. Educators can also use this tool to monitor their students' progress and provide timely support sessions.[10]

Limitations of AI

Despite the plethora of positivity and adaptation that AI brings to dentistry, we need to be mindful of the challenges and limitations that it poses. The main ethical concern that AI raises is data protection. The General Dental Council (GDC) mandates that all registered professionals must: "Maintain and Protect Patients information" as part of their nine standards.[19] Similarly, the General Data Protection Regulations Act (GDPR) 2018 emphasises the necessity to handle patient data securely and fairly.[20]

AI will utilise extensive datasets like medical histories, dental histories, patient details and case studies to analyse radiographs and provide treatment plans to achieve the outcomes mentioned. It should be stressed that clinicians using AI technologies are aware of the risks involved with AI data breaches and understand how to use data responsibly. Transparency with the patient is imperative. Individuals must be informed on how their data will be used and the risks that may arise. This is essential to obtain valid consent and maintain a level of trust and rapport.

Conclusion

It raises no doubt that AI possesses the ability to enhance patient care and satisfaction within dentistry by allowing dental professionals to work more effectively. AI has already made a lasting impact and the future is promising. It can be argued that AI is making significant advancements in the diagnostic aspect of dentistry, shifting the focus towards a more preventive and minimally invasive approach. As many more dental practices and schools look to implement AI, it is

pertinent to be cautious and ensure that the patient's best interests and protection remain at the heart of dentistry. Dental students must keep up to date on advancements within AI as these developments will undoubtedly influence their education and future practice.

Minha Chowdhury

Hi, my name is Minha Chowdhury, and I am a second-year dental student at Peninsula Dental School. Writing this article on artificial intelligence and its potential applications in dentistry has been an exciting experience. I hope you find it as enjoyable and interesting to read as I did to write!

References

1. McAleer K. AI is the new electricity: insights from Dr. Andrew Ng [Internet]. UC Berkeley Sutardja Center. 2023 [cited 2024 May 1]. Available from: https://scet.berkeley.edu/ai-is-the-new-electricity-insights-from-dr-andrew-ng/
2. UK Government. Artificial intelligence . www.great.gov.uk. 2023 [cited 2024 May 1]. Available from: https://www.great.gov.uk/campaign-site/uk-na-innovation/sectors/artificial-intelligence/
3. Salehi H, Burgueño R. Emerging artificial intelligence methods in structural engineering. Engineering Structures. 2018 Sep 15;171(171):170–89.
4. Walls, N. Radiography update. Vital 9, 31 (2012). https://doi.org/10.1038/vital1521
5. NHS . X-ray [Internet]. NHS. NHS; 2022 [cited 2024 May 2]. Available from: https://www.nhs.uk/conditions/X-ray/
6. Faculty of General Dental Practice (UK) and Public Health England, 2020. Guidance notes for dental practitioners on the safe use of X-ray equipment. 2nd ed. [online] Available at: https://www.rqia.org.uk/RQIA/files/44/449bd-d1c-ccb0-4322-b0df-616a0de88fe4.pdf [Accessed 2 May 2024].
7. Rushton VE, Horner K, Worthington HV. The quality of panoramic radiographs in a sample of general dental practices. British Dental Journal. 1999 Jun;186(12):630–3.
8. Dentistry. The sweet spot for AI and dental imaging technology [Internet]. 2024 [cited 2024 May 3]. Available from: https://dentistry.co.uk/2024/01/25/the-sweet-spot-for-ai-and-dental-imaging-technology/
9. Gupta J, Ali SP. Cone beam computed tomography in oral implants. National Journal of Maxillofacial Surgery. 2013;4(1):2.
10. Dhopte A, Bagde H. Smart smile: revolutionizing dentistry with artificial intelligence. Cureus. 2023 Jun 30;15(6).
11. Mamat R, Nik Abdul Ghani NR. The complexity of the root canal anatomy and its influence on root canal debridement in the apical region: a review. Cureus. 2023 Nov 18;15(11):e49024.
12. Pietrzycka K, Pawlicka H. Clinical aspects of pulp stones: a case report series. Dental and Medical Problems. 2020 Apr 1;57(2):213–20.
13. Aminoshariae A, Kulild J, Nagendrababu V. Artificial intelligence in endodontics: current applications and future directions. Journal of Endodontics. 2021 Jun;47(9).
14. NHS England. NHS dental statistics for England, 2022-23, Annual report [Internet]. NHS Digital. 2023 [cited 2024 May 3]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-dental-statistics/2022-23-annual-report
15. Schwebel FJ, Larimer ME. Using text message reminders in health care services: A narrative literature review. Internet Interventions. 2018 Sep;13(13):82–104.
16. Shaikh K, Bekal VS, Ahmed Marei HF, Moustafa Elsayed WS, Surdilovic D, Jawad LA. Artificial intelligence in dentistry. Springer Nature; 2022. Chapter 5, Advancements in dentistry; p.123-126.
17. Moussa R, Alghazaly A, Althagafi N, Eshky R, Borzangy S. Effectiveness of virtual reality and interactive simulators on dental education outcomes: systematic review. European Journal of Dentistry. 2021 Aug 24;16(1).
18. Jian MJKO. Personalized learning through AI. Advances in Engineering Innovation. 2023 Dec;5.
19. General Dental Council. General Dental Council - Focus on standards [Internet]. gdc-uk.org. 2013 [cited 2024 May 3]. Available from: https://standards.gdc-uk.org/
20. GOV.UK. Data Protection Act [Internet]. Gov.UK. 2018 [cited 2024 May 3]. Available from: https://www.gov.uk/data-protection

Review

Can inhibitors of JAK1 be used as an effective treatment for type 1 diabetes?

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Abstract

HLA-I hyperexpression on β-cells is a key feature of type 1 diabetes mellitus (T1DM) and increases visibility towards cytotoxic T cells. Modulating HLA-I expression by disrupting the JAK/STAT signalling pathway has been proposed as an attractive target. JAK1 is particularly interesting for its role as a signal transducer in multiple IFN induced pathways. This review will evaluate whether inhibitors of JAK1 could be used as an effective treatment for T1DM. Preclinical evidence suggests that JAK1 inhibitors can decrease the hallmarks of T1DM. Clinical evidence also indicates improved glycaemic control and decreased exogenous insulin requirements in T1DM patients. JAK1 inhibitors may also reduce biomarkers of diabetic kidney disease, thus widening the therapeutic window of treatment in patients. JAK1/2 inhibitors like Baricitinib have already been used clinically in the treatment of rheumatoid arthritis safely. However, individuals with T1DM are at increased risk of adverse effects. The duration of treatment in T1DM is likely significantly longer than other autoimmune conditions and may lead to severe anaemia. Thus, longitudinal studies are required to identify the long-term safety of JAK1 inhibitors. The ongoing JAKPOT trial investigating a JAK1 specific inhibitor could provide more evidence on the future of T1DM management.

Abbreviations

DKD – diabetic kidney disease
ER – endoplasmic reticular
HLA-1 – human leukocyte antigen-1
NOD – non-obese diabetic
T1DM – type 1 diabetes mellitus

Introduction

Type 1 diabetes

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterised by the infiltration of CD8+ T cells among other immune cells into the pancreatic islets of Langerhans.[1] These immune cells selectively target insulin-secreting β-cells which results in in loss of β-cell mass and function. Consequently, individuals with T1DM have decreased endogenous insulin production and suffer from impaired glucose homeostasis. These individuals are therefore required to monitor their blood sugar and administer daily exogenous insulin injections to manage their blood glucose levels. Nevertheless, individuals may still experience inadequate glycaemic regulation and are at risk of nephropathy, neuropathy and cardiovascular complications.[1] It has also been reported that 38% of people with T1DM have experienced severe hypoglycaemia due to hypoglycaemic unawareness, which may cause seizures and brain damage.[2]

T1DM is a condition of growing concern. It is estimated that 8.4 million people are currently living with T1DM globally. However, this figure is expected to rise to 13.5-17.4 million by 2040.[1,3] As such, novel

treatment strategies that modify disease state rather than manage the disease may be an attractive solution to the rising economic and public health burden of T1DM. Furthermore, these alternative therapeutics could potentially address the limitations of current T1DM treatments.

JAK/STAT signalling

Interestingly, increased expression of the immune recognition complex human leukocyte antigen I (HLA-I) has been identified on the surface of β-cells in T1DM patients but not in people without diabetes.[1,4] This has led researchers to investigate whether therapeutics could slow down T1DM development by preventing β-cell death via immunomodulation.

It has been suggested that HLA-1 hyperexpression in T1DM is driven via type I, II, III interferon signalling following viral infection via the JAK/STAT pathway. Although JAKs are a family of tyrosine kinases (JAK1, JAK2, JAK3, TYK2), JAK1 is a common denominator in the signal transduction of all three of these interferons.[5,6] As such, inhibitors of JAK1 could prevent downstream signalling via multiple pathways (**Figure 1**). Therefore, the aim of this review is to evaluate if inhibitors of JAK1 could be used as an effective treatment in T1DM. It will also explore the safety profile of these drugs.

Method

PubMed and TRIP databases were used to identify the literature for this review. Searching for the terms ((Type 1 Diabetes) AND ((JAK inhibitor) OR (JAK1 inhibitor)) generated 334 papers (**Figure 2**). Eligibility of these papers was assessed by screening the title and abstract for relevancy. Inclusion criteria were articles that focused on T1DM and inhibitors of JAK1. Exclusion criteria were incomplete articles and papers published before 2010 due to the novelty of this research. This resulted in 14 papers being used for discussion.

Discussion

Preclinical effects on β-cell function

Inhibitors of JAK1 have been used on T1DM models with positive results.[5-10] Despite the differences in T1DM models amongst the studies, these inhibitors were found to significantly decrease hallmarks of T1DM, namely, HLA-I hyperexpression, insulitis, and endoplasmic reticular (ER) stress (**Table 1**). However, these studies found that HLA-I is re-upregulated after ceasing treatment. This implies that individuals will need persistent exposure to inhibitors of JAK1 for the treatment to be effective.

Ge et al found that LN3103801 was able to decrease IFN- γ induced HLA-I hyperexpression and prevent diabetes in non-obese diabetic (NOD) mice before and after administering anti-PD-L1.[8] The same results were also seen after hyperglycaemia onset, suggesting JAK1 inhibitors could be used after T1DM onset. Although, a study found that EndoC-βH1 cells treated with Baricitinib after being exposed to IFN- α did not affect HLA-I hyperexpression.[9] This is significant as JAK inhibitors prevent β-cell death by disrupting immune cell interaction. However, symptoms of T1DM typically presents after a critical mass of β-cells have been destroyed.[1] Therefore, it is important to identify the window in which these drugs prevent targeted β-cell destruction. Notably, Ge et al induced diabetes via anti-PD-L1 which is not typical of T1DM pathogenesis and may explain the different results. However, these studies used different model organisms, dosages and JAK1/2 inhibitors, which limits comparability.

Importantly, inhibitors of JAK1 seemed more effective than other classes of JAK inhibitors such as TYK2. Dos Santos et al identified that Baricitinib and Ruxolitinib (both JAK1/2 inhibitors) were less potent inhibitors of HLA-1 upregulation than TYK2 inhibitors.[10] Despite this, JAK1/2 inhibitors were able to inhibit ER stress markers unlike TYK2 inhibitors. This indicates that JAK1/2 inhibitors could work two-fold by preventing both targeted β-cell destruction and dysfunction. However, the clinical implications of this have not been investigated. Clinical effects on β-cell function

JAK1 specific inhibitors have yet to be investigated in humans with T1DM. However, the use of JAK1/2 inhibitors in a STAT1 gain of function case study has served as foundational evidence for its clinical use.[11] A 15-year-old boy with T1DM was given Ruxolitinib after presenting with chronic mucocutaneous candidiasis. Twelve months after starting Ruxolitinib treatment, the individual discontinued exogenous insulin therapy and was normoglycemic until the end of the study 12 months later. More interestingly, the patient was given Ruxolitinib 9 months after being diagnosed with T1DM, well past the "honeymoon period" in which β-cell function can be temporarily restored. Follow up of this individual could be beneficial in determining whether these effects are long lasting. This study is supported by another case report whereby Baricitinib improved glycaemic control in a 71-year-old patient with slowly progressive T1DM.[12] Shortly after beginning Baricitinib therapy, the individual's daily exogenous insulin requirements decreased by 35% and this was maintained for the duration of the 52-week trial. These studies suggest the possibility that T1DM can be improved and perhaps even reversed in humans. However, these studies are limited by their small sample size (n=1) and their atypical T1DM profiles.

Recently, the BANDIT trial, a phase 2, double blind, randomised controlled trial (n=91) explored whether Baricitinib could preserve β-cell function and improve metabolic markers compared to placebo.[13] Mean c-peptide levels were used to measure β-cell function. Patients (10-30 years old) who had been recently diagnosed (<100 days) with T1DM were orally administered Baricitinib daily for 48 weeks. Patients taking Baricitinib showed sustained levels of c-peptide, indicating maintained insulin secretion for the duration of the trial. Additionally, individuals required 21% less exogenous insulin on average. However, several limitations were identified. The sample population consisted primarily of white individuals (88%) older than 10 years without any pre-existing conditions such as cytopenia or history of thrombosis. Therefore, this study cannot be generalised to other demographics. Given the juvenile onset of T1DM, a cohort with younger individuals could also better reflect the intended target population and provide insight into the efficacy of Baricitinib. Additionally, the relatively short trial (48 weeks) did not determine the long-term effects of this treatment. Seeing as T1DM is a chronic condition, long-term follow up could reveal the sustained effects of this intervention.

Treating diabetic complications

The immunomodulatory and anti-inflammatory effects of JAK inhibitors have also been investigated in the treatment of diabetic complications.[14-16] This could potentially widen the therapeutic window for individuals who no longer have sufficient functional β-cell reserves. Two studies investigating whether Baricitinib could modulate markers of diabetic kidney disease (DKD) found similar results. After 24 weeks, a phase 2 randomised control trial (n=129) found that Baricitinib significantly reduced inflammatory cytokine levels in the blood and urine. Compared to placebo, they also identified a 40% decrease in albumin to creatine ratio in urine, a gold standard in measuring DKD.[14] Similarly, Curovic et al (n=26) identified decreased urinary albumin-creatine ratio when Baricitinib was taken in rotation with three other non-JAK inhibiting drugs.[15] However, this study found that Baricitinib only worked in 13% of individuals and was the least effective of the four drugs at lowering urinary albumin to creatinine ratio. Interestingly, patients with T1DM responded best to Baricitinib compared to type 2 diabetes.[15] This suggests that individualisation of treatment could have potential in T1DM patients. However, the study is limited by the small sample size and short treatment duration of only 4 weeks. Baricitinib was also investigated to treat cardiovascular neuropathy in humans.[16] However, this study did not identify any significant results. Although, this study did not contain a control group and was at risk of a carry-over effect from a

previous crossover trial.

Safety profile

The safety profile of JAK1/2 inhibitors in T1DM management is mixed. Baricitinib, a JAK1/2 inhibitor has been safely used in humans as a treatment for rheumatoid arthritis and atopic dermatitis.[17] However, this study identified that individuals with rheumatoid arthritis and diabetes mellitus compared to individuals with just rheumatoid arthritis were at significantly higher risk of major adverse cardiovascular events, venous thromboembolism, serious infection and mortality. Therefore, patient disease status and response to treatment should be considered when treating patients with Baricitinib. Tuttle et al (n=129) also identified anaemia in 32% of T1DM patients taking Baricitinib compared to 3.7% of patients in the control group.[14] Interestingly, the BANDIT trial did not identify a higher risk of adverse drug reactions compared to placebo.[13] However, this may be due to the small sample size and short duration of the trial. Additionally, the study excluded individuals with anaemia and thrombosis who may be at higher risk of adverse events.

Although JAK inhibitors seem surprisingly well tolerated for drugs that disrupt important pathways involved in processes such as immunity,[14] longer duration of treatment may lead to more severe anaemia or infection. It is important to consider that the duration of drug persistence in treating either T1DM or DKD would likely be greater than the duration of these studies. Therefore, longitudinal trials could be done to assess the long-term safety and efficacy of Baricitinib in managing T1DM clinically. Interestingly, erythropoietin signals through JAK2 dependent pathways.14 Therefore, the risk of anaemia and additional off-target effects could potentially be reduced by using a selective JAK1 inhibitor. The JAKPOT trial will in part investigate Abrocitinib, a specific JAK1 inhibitor in recently diagnosed T1DM patients.[18] However, this study faces many of the same limitations in identifying adverse drug reactions as the BANDIT trial, such as small sample size (n=78). Additionally, it is unclear whether individuals with co-existing conditions are eligible for the trial.

Conclusion

Inhibitors of JAK1 as an adjuvant in treating T1DM is promising. However, the lack of young patients in clinical trials means that results cannot be generalised to a significant proportion of individuals with T1DM. Furthermore, the lack of standardisation among studies using JAK inhibitors makes it difficult to determine if there is an optimal delivery route, dosage, or type of JAK1 inhibitor in T1DM treatment. Future studies should investigate the long-term effects and safety of JAK1 specific inhibitors in T1DM treatment.

References

1. Lucier J, Mathias PM. Type 1 diabetes [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Feb 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507713/.
2. Corrales PJP, Arias Lozano C, Jiménez Martínez C, López Jiménez LM, Sirvent Segovia AE, García Blasco L, et al. Prevalence of severe hypoglycemia in a cohort of patients with type 1 diabetes. Endocrinol Diabetes Nutr (Engl Ed). 2021;68(1):47-52. doi:10.1016/j.endinu.2020.01.002
3. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 2022;10(10):741-60. doi:10.1016/s2213-8587(22)00218-2
4. Russell MA, Richardson SJ, Morgan NG. The role of the interferon/JAK-STAT axis in driving islet HLA-I hyperexpression in type 1 diabetes. Front Endocrinol (Lausanne). 2023;14:1270325. doi:10.3389/fendo.2023.1270325
5. Colli ML, Ramos-Rodríguez M, Nakayasu ES, Alvelos MI, Lopes M, Hill JLE, et al. An integrated multi-omics approach identifies the landscape of interferon-α-mediated responses of human pancreatic beta cells. Nat Commun. 2020;11(1):2584. doi:10.1038/s41467-020-16327-0
6. Ge T, Jhala G, Fynch S, Akazawa S, Litwak S, Pappas EG, et al. The JAK1 selective inhibitor ABT 317 blocks signaling through interferon-γ and common γ chain cytokine receptors to reverse autoimmune diabetes in NOD mice. Front Immunol. 2020;11:588543. doi:10.3389/fimmu.2020.588543
7. Trivedi PM, Graham KL, Scott NA, Jenkins MR, Majaw S, Sutherland RM, et al. Repurposed JAK1/JAK2 inhibitor reverses established autoimmune insulitis in NOD mice. Diabetes. 2017;66(6):1650-60. doi:10.2337/db16-1250
8. Ge T, Phung AL, Jhala G, Trivedi P, Principe N, De George DJ, et al. Diabetes induced by checkpoint inhibition in nonobese diabetic mice can be prevented or reversed by a JAK1/JAK2 inhibitor. Clin Transl Immunology. 2022;11(11):e1425. doi:10.1002/cti2.1425
9. Coomans de Brachène A, Dos Santos RS, Marroqui L, Colli ML, Marselli L, Mirmira RG, et al. IFN-α induces a preferential long-lasting expression of MHC class I in human pancreatic beta cells. Diabetologia. 2018;61(3):636-40. doi:10.1007/s00125-017-4536-4
10. Dos Santos RS, Guzman-Llorens D, Perez-Serna AA, Nadal A, Marroqui L. Deucravacitinib, a tyrosine kinase 2 pseudokinase inhibitor, protects human EndoC-βH1 β-cells against proinflammatory insults. Front Immunol. 2023;14:1263926. doi:10.3389/fimmu.2023.1263926
11. Chaimowitz NS, Ebenezer SJ, Hanson IC, Anderson M, Forbes LR. STAT1 gain of function, type 1 diabetes, and reversal with JAK inhibition. N Engl J Med. 2020;383(15):1494-6. doi:10.1056/NEJMc2022226
12. Fujita Y, Nawata M, Nagayasu A, Someya K, Saito K, Tanaka Y. Fifty-two-week results of clinical and imaging assessments of a patient with rheumatoid arthritis complicated by systemic sclerosis with interstitial pneumonia and type 1 diabetes despite multiple disease-modifying antirheumatic drug therapy that was successfully treated with Baricitinib: a novel case report. Case Rep Rheumatol. 2019;2019:5293981. doi:10.1155/2019/5293981
13. Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJ, et al. Baricitinib and β-cell function in patients with new-onset type 1 diabetes. N Engl J Med. 2023;389(23):2140-50. doi:10.1056/NEJMoa2306691
14. Tuttle KR, Brosius FC, 3rd, Adler SG, Kretzler M, Mehta RL, Tumlin JA, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. Nephrol Dial Transplant. 2018;33(11):1950-9. doi:10.1093/ndt/gfx377
15. Curovic VR, Jongs N, Kroonen M, Zobel EH, Hansen TW, Sen T, et al. Optimization of albuminuria-lowering treatment in diabetes by crossover rotation to four different drug classes: a randomized crossover trial. Diabetes Care. 2023;46(3):593-601. doi:10.2337/dc22-1699
16. Laursen JC, Rotbain Curovic V, Kroonen M, Jongs N, Zobel EH, Hansen TW, et al. Effects of baricitinib, empagliflozin, linagliptin and telmisartan on cardiovascular autonomic neuropathy in type 1 diabetes: An exploratory, randomized, open-label, crossover trial. Diabetes Obes Metab. 2023;25(10):3064-7. doi:10.1111/dom.15180
17. Taylor PC, Bieber T, Alten R, Witte T, Galloway J, Deberdt W, et al. Baricitinib safety for events of special interest in populations at risk: analysis from randomised trial data across rheumatologic and dermatologic indications. Adv Ther. 2023;40(4):1867-83. doi:10.1007/s12325-023-02445-w
18. TrialNet. JAK inhibitors newly diagnosed study (JAKPOT T1D) [Internet]. 2024 [cited 2024 Feb 25]. Available from: https://www.trialnet.org/our-research/newly-diagnosed-t1d/jakpot-t1d

Lucas Gadaleta

Hi, I am Lucas, a second-year medical student at the University of Exeter. This article was written as part of a student selected component which enabled me to develop my interest in endocrinology. Notably, this experience enabled me to participate in research that is trying to better understand and characterise type 1 diabetes aetiology. My other passion lies in following a career in orthopaedics, a unique specialty where you can deliver both life improving care and play with power tools.

Table 1. Inhibitors of JAK1

Inhibitor	Outcome	Model	Study
AZD 1489 (JAK1/2 inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Prevented development of T1D Reversed diabetes in newly diagnosed NOD mice	NOD mice Human islets	Trivedi et al[7]
ABT 317 (JAK1 selective inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Reversed diabetes in newly diagnosed NOD mice	NOD mice	Ge et al[6]
LN3103801 (JAK1/2 inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Prevented anti-PD-L1 induced diabetes	NOD mice	Ge et al[8]
Ruxolitinib (JAK1/2 inhibitor)	- Decreased HLA-I upregulation - Decreased ER stress markers	EndoC-βH1 β-cells	Coomans de brachene et al[9]
Baricitinib (JAK1/2 inhibitor)	- Decreased HLA-I upregulation - Decreased ER stress markers - Prevented beta cell apoptosis	EndoC-βH1 β-cells Human islets	Colli et al[5]
Baricitinib & *Ruxolitinib*	- Decreased HLA-I upregulation - Decreased ER stress markers	EndoC-βH1 β-cells	Dos Santos et al[10]

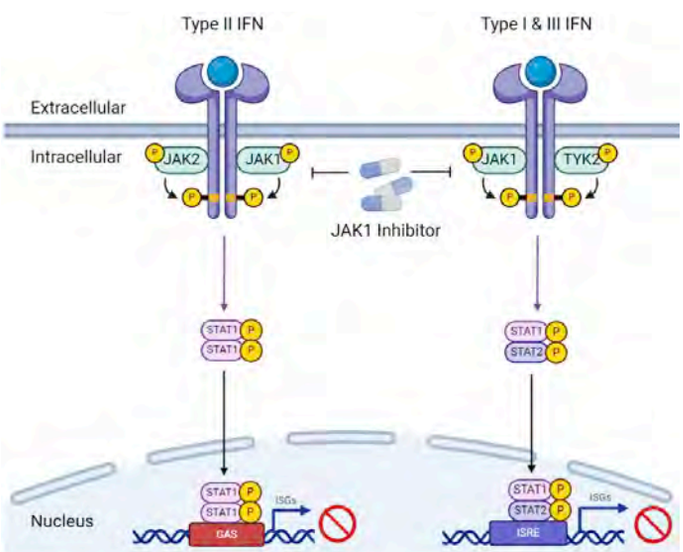

Figure 1. JAK1 inhibitor mechanism of action. Type II IFN signals via JAK1/JAK2 whereas type I & III signal via JAK1/JAKIII. JAK1 inhibitors target a common element to both signalling pathways to modulate downstream signalling. This results in decreased expression of interferon stimulated genes (ISGs). JAK (Janus kinase); STAT (Signal transducers and activators of transcription); GAS(Gamma interferon activation site); ISRE (Interferon stimulated response element). Adapted from Russell, Richardson, Morgan (2023),[4] with thanks, using Biorender.

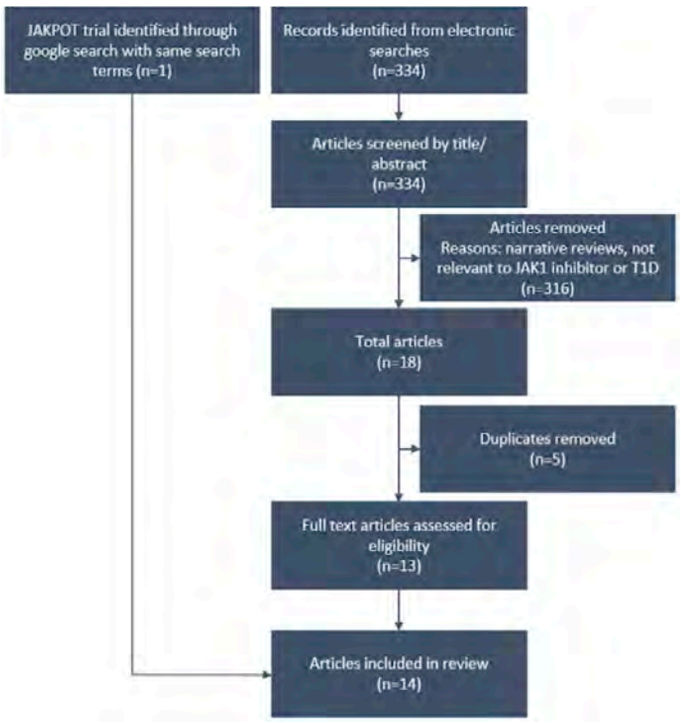

Figure 2. PRISMA diagram. Workflow for literature search and selection.

Review

Non-pharmacological treatments used to enhance sleep quality for patients experiencing sleep disturbances caused by chronic pain

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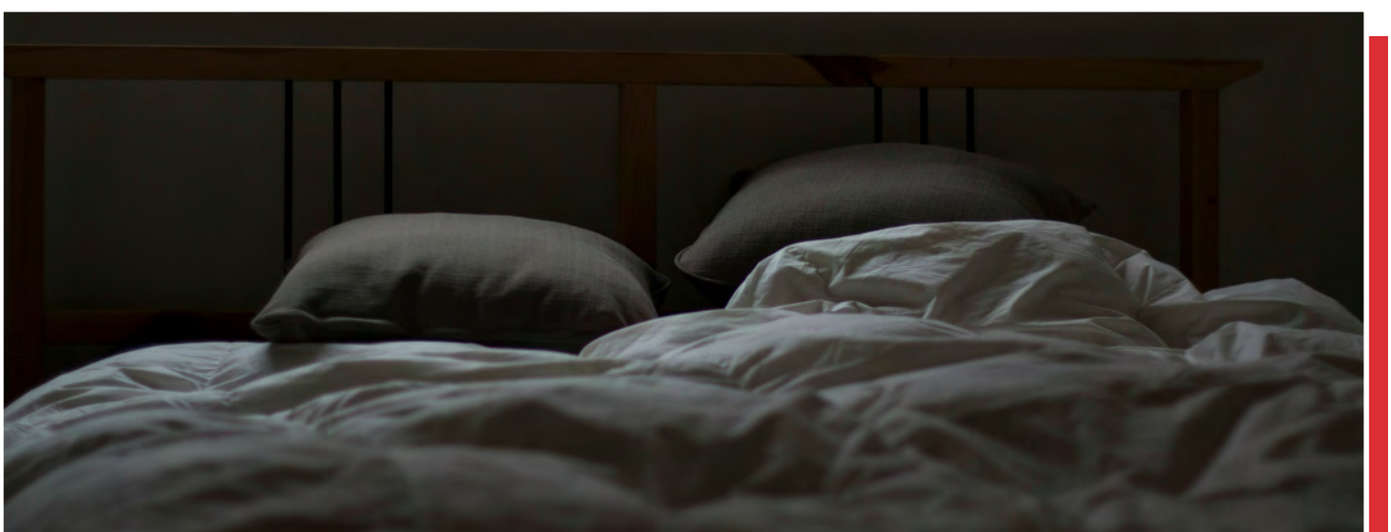


Abstract

Chronic pain poses a significant burden on healthcare systems globally. It is often accompanied by sleep disturbances which further exacerbate a patient's condition, and therefore chronic pain can have a substantial impact on individuals' holistic health and wellbeing. This article explores the bidirectional relationship between chronic pain and sleep disturbances, before discussing three non-pharmacological aids that are recommended by NICE to treat chronic pain: cognitive behavioural therapy, exercise programmes and acupuncture. The efficacy of these various approaches is explored by assessing the latest evidence, which highlights the importance of implementing a multimodal approach that combines non-pharmacological aids to optimise patient outcomes.

Abbreviations

CBT-I - Cognitive Behavioural Therapy for Insomnia
GP - general practitioner
NSAIDS - non-steroidal anti-inflammatory drugs
PSQI - Pittsburgh Sleep Quality Index
RCT - Randomised Controlled Trial

Introduction

Pain serves as the predominant reason for individuals seeking medical care, with three of the ten modal presentations being chronic: back pain, osteoarthritis and headaches.[1] Chronic pain, as defined by NICE guidelines, is pain that persists or recurs for more than three months.[2] This makes it no surprise that individuals experiencing chronic pain may also experience a sleep related issue. The relationship between sleep quality and chronic pain is a bidirectional one; pain can negatively impact sleep e.g. by making it difficult to fall asleep and increase awakenings, and a reduced sleep duration and quality can increase spontaneous pain and lower pain thresholds.[3] A systematic literature search evaluating the effect of sleep changes on subsequent pain-related outcomes established 16 longitudinal studies comprising 61,000 participants.[4] Results indicated a decline in sleep quantity and quality was associated with a two-to-three-fold increase of developing a pain condition.

Within healthcare, 88.9% of individuals attending a university pain clinic reported at least one sleep complaint, with over 65% regarding themselves as poor sleepers.[5,6] Considering the annual incidence rate of chronic pain in the UK being 8.3% with a recovery rate of 5.3%, evidenced by a large scale 4-year longitudinal study,[1] it is vital those affected gain a better understanding of the importance good sleep quality has on recovery. To combat this, healthcare workers recommend both pharmacological and non-pharmacological treatments. However, due to the range of potential risks associated with pharmacological treatment such as dependence, tolerance and withdrawal, non-pharmacological treatment is the preferred starting point.[7] Furthermore, the range of non-pharmacological treatments is extensive and has been well documented to improve sleep hygiene.[8] NICE guidelines identified cognitive behavioural therapy, exercise programmes and acupuncture as non-pharmacological treatments for chronic pain,[2] so each of these will be explored in this article.

CBT-I

A meta-analysis evaluating the efficacy of non-pharmacological treatments for patients suffering with insomnia induced by chronic pain identified nine randomised control trials which found Cognitive Behavioural Therapy for Insomnia (CBT-I) as the main treatment plan.[9] CBT-I is a comprehensive treatment that addresses various aspects of insomnia by targeting behavioural, cognitive and physiological factors, and is typically conducted over 4–8 individual or group sessions. It aims to adjust and change maladaptive behaviours and misconstrued beliefs about sleep and insomnia.[10] Furthermore, CBT-I is the first line of treatment for individuals with insomnia caused by chronic pain, backed by the guidelines for chronic insomnia management.[11] These suggest that CBT-I provides better overall value compared to pharmacological interventions, as it poses fewer risks and has a stronger base for its benefits. Also, a systematic review indicated that pharmacological approaches to managing chronic pain show only minor impacts on reducing pain.[10] However, it may be imperative to address other interconnected symptom clusters, such as sleep disturbances, which also play a role in the persistence and severity of chronic pain, to enhance outcomes in pain management. Four randomised control trials (RCTs) examined the effectiveness of CBT-I in reducing insomnia and pain symptoms.[10] Overall, the results exhibit medically relevant enhancements in sleep symptoms. However, the results for pain management were inconsistent. Although the results showed advancements in pain-related outcomes within functional areas, including pain interference and disability, there was only limited evidence backing the short-term effectiveness for pain severity. Therefore, it is plausible to use CBT-I in conjunction with other treatments.

Exercise

A common pharmacological treatment for chronic pain is long-term use of non-steroidal anti-inflammatory drugs (NSAIDS).[12] Although relatively safe for short-term use, they carry implications when taken long term, and one study recorded they are responsible for 30% of hospital admissions for adverse drug reactions, including renal damage, gastrointestinal bleeding, strokes and myocardial infarction.[12] A relatively safe and inexpensive alternative method of enhancing sleep quality is via exercise. Exercise has been supported by the 'National Sleep Foundation' and regularly features in sleep hygiene recommendations.[6] Research indicates that multimodal exercise regimens, incorporating a variety of activities have demonstrated efficacy in notably alleviating pain associated with the chronic pain conditions, chronic lower back pain, fibromyalgia, osteoarthritis and rheumatoid arthritis.[13] Furthermore, regular engagement in aerobic exercise has shown comparable effectiveness to NSAIDs in reducing pain.[13] More specifically, in fibromyalgia patients, a meta-analysis of RCTs examining movement therapies reported substantial improvements in sleep among 372 subjects.[13] Whilst research indicates that participating in exercise enhances sleep quality, the effect is reciprocal. Without a deliberate intervention, 119 chronic pain patients demonstrated a natural increase in exercise levels on days following nights of higher quality sleep. This suggests a promising build-up of events that should improve sleep quality in patient with chronic pain overtime.

Within healthcare, an 8 week 'quasi-experimental single group pretest-posttest design' was conducted by physiotherapists and nurses on the effect of light exercise in older adults experiencing chronic pain, including balancing, strengthening, stretching and towel dancing.[14] The study group consisted of 75 participants living in a nursing home, of which 73% had stated consistent pain in the previous 3 months. Pain intensity was collected before and after the programme using a 10-point scale. Before the programme the average pain score was 4.89, with a 2-point decrease post programme being 2.89. Although, this experiment was subjected to older adults, overall evidence suggests regular exercise is beneficial to those living with chronic pain. Therefore, it is important for healthcare workers to educate those with chronic pain on the benefits of staying physically active, as well as adapting to the type of exercise that is safe for them to bear, as treatment for pain management.

Another healthcare study suggested exercise is a 'core' treatment for chronic knee pain, however general practitioners (GPs) do not recommend it enough.[15] A cross-sectional study surveyed 835 UK GPs to investigate the use of exercise in patient treatments.[15] 87% reported they would use exercise as an intervention, suggesting many GPs believe it has value in treating patients. However, there is evidence to suggest the utilisation of exercise for patients by GPs is linked to their attitudes and beliefs, regarding their perception of their role, responsibilities and competence in initiating exercise.[15] This implies some GPs may doubt the perceived efficacy of exercise in treating chronic pain, which could be down to many factors such as time constraints and perceived patient compliance to the treatment plan. Additionally, patients face social barriers when it comes to non-pharmacological treatment such as exercise, including high costs, lack of transport and lack of motivation.[16] This makes them less likely to comply to the treatment, limiting their condition from improving. Therefore, it is of high value that these resources are included as part of their treatment plan by the healthcare.

Acupuncture

Acupuncture has been one of the oldest and most frequently used medical procedures for treatment of chronic conditions since being discovered in China over 2500 years ago.[17] It involves symptom relief by inserting needles at specified areas of the body. An increasing amount of research has shown that acupuncture could enhance various physical conditions associated with chronic pain, including fibromyalgia, headaches and musculoskeletal pain.[17]

A 10-week randomised clinical trial compared acupuncture with usual care for improvement in sleep quality in cancer survivors with clinically significant chronic musculoskeletal pain and sleep disturbance.[18] The usual care included analgesic medications, glucocorticoid injections and physical therapy. On the other hand, the acupuncture treatment consisted of both auricular acupuncture and electroacupuncture. Auricular acupuncture is specific to the ear region, whilst electroacupuncture combines traditional acupuncture of the body with electrical stimulation.[18] The assessment of sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI) global score.[18] PSQI assesses seven key aspects of sleep: subjective sleep quality, sleep latency, sleep efficiency, sleep duration, sleep disturbances, use of sleep medication and daytime dysfunction.[19] The PSQI global score is derived by summing the scores of these seven components and ranges from 0 to 21, with higher scores reflecting poorer sleep quality, with a cut-off of at least six points indicating poorer sleep quality. Moreover, a systematic literature search identified 49 studies evaluating different sleep quality questionnaires.[19] The results stated PSQI was the most widely used questionnaire for subjective sleep quality, showing good reliability and validity.

The findings from the 10-week randomised clinical trial showed both types of acupuncture significantly improved sleep quality, with patients who had auricular acupuncture PSQI score being 1.59 points lower than the usual care patients, and patients who had electroacupuncture average PSQI score being 1.42 points lower than the usual care patients.[18] This indicates that pain relief from acupuncture potentially improves sleep quality in cancer patients with chronic pain, compared to those that had usual treatment.

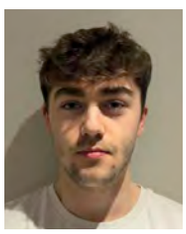
Conclusion

In the US alone, the estimated annual cost of care and treatment for chronic pain is approximately $650 billion.[20] Due to the high financial burden chronic pain has within healthcare, it is vastly important for resource allocation in this area. The management of sleep disturbances in chronic pain patients is crucial for enhancing these patients' recovery. CBT-I, exercise, and acupuncture have each

been proven to help aid this process. Nonetheless, although each of the three non-pharmacological treatments have been established as effective, it may be beneficial to not rely on them independently, but to be used in conjunction with other treatments for a more effective outcome.

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-2097. doi: 10.1016/S0140-6736(21)00393-7. PMID: 34062143.
2. NICE. NICE recommends range of effective treatments for people with chronic primary pain and calls on healthcare professionals to recognise and treat a person's pain as valid and unique to them. 2021. Available from: https://www.nice.org.uk/news/article/nice-recommends-range-of-effective-treatments-for-people-with-chronic-primary-pain-and-calls-on-healthcare-professionals-to-recognise-and-treat-a-person-s-pain-as-valid-and-unique-to-them
3. Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. Sleep Med Rev. 2020;45:1-10. doi: 10.1016/j.smrv.2020.101376. PMID: 32151755.
4. Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. Sleep. 2018;41(6):1-15. doi: 10.1093/sleep/zsy038. PMID: 29635380.
5. McCracken LM, Iverson GL. Disrupted sleep patterns and daily functioning in patients with chronic pain. Pain. 2002;99(3):207-215. doi: 10.1016/S0304-3959(02)00101-X. PMID: 12406516.
6. Tang NKY. Insomnia Co-occurring with chronic pain: clinical features, interaction, assessments and possible interventions. J Clin Psychol. 2008;64(8):947-967. doi: 10.1002/jclp.20496. PMID: 18442000.
7. Lowe H, Haddock G, Mulligan LD, Gregg L, Fuzellier-Hart A, Carter LA, Kyle SD. Does exercise improve sleep for adults with insomnia? A systematic review with quality appraisal. Br J Sports Med. 2019;53(10):654-662. doi: 10.1136/bjsports-2018-099488. PMID: 30467114.
8. Ostovar-Kermani T, Arnaud D, Almaguer A, Garcia I, Gonzalez S, Martinez YHM, Surani S. Painful sleep: insomnia in patients with chronic pain syndrome and its consequences. Pain Res Manag. 2020;2020:1-9. doi: 10.1155/2020/7293907. PMID: 32983612.
9. Chan NY, Chan JWY, Li SX, Wing YK. Non-pharmacological approaches for management of insomnia. Front Neurol. 2021;12:678450. doi: 10.3389/fneur.2021.678450. PMID: 34267578.
10. Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-behavioral therapy for comorbid insomnia and chronic pain. Sleep Med Rev. 2014;18(6):555-567. doi: 10.1016/j.smrv.2014.03.003. PMID: 24745608.
11. Koffel E, Amundson E, Wisdom JP. Exploring the meaning of cognitive behavioral therapy for insomnia for patients with chronic pain. Pain Med. 2020;21(8):1497-1504. doi: 10.1093/pm/pnz274. PMID: 31816015.
12. Davis A, Robson J. The dangers of NSAIDs: look both ways. BMJ. 2016;353:i2350. doi: 10.1136/bmj.i2350. PMID: 27170552.
13. Ambrose KR, Golightly YM. Physical exercise as non-pharmacological treatment of chronic pain: Why and when. Best Pract Res Clin Rheumatol. 2015 Feb;29(1):120-30. doi: 10.1016/j.berh.2015.04.022. Epub 2015 May 23. PMID: 26267006; PMCID: PMC4534717.
14. Tse MMY, Wan VTC, Ho SSK. Physical exercise: does it help in relieving pain and increasing mobility among older adults with chronic pain? J Clin Nurs. 2011;20(5-6):635-644. doi: 10.1111/j.1365-2702.2010.03379.x. PMID: 21114609.
15. Cottrell E, Roddy E, Rathod T, Porcheret M, Foster NE. What influences general practitioners' use of exercise for patients with chronic knee pain? Results from a national survey. BMC Fam Pract. 2016;17:121. doi: 10.1186/s12875-016-0520-9. PMID: 27491862.
16. Becker WC, Dorflinger L, Edmond SN, Islam L, Heapy AA, Fraenkel L. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. Pain Med. 2017;18(5):889-902. doi: 10.1093/pm/pnw217. PMID: 27794119.
17. Hull A, Reinhard M, McCarron K, Allen N, Jecmen MC, Akhter J, Duncan A, Soltes K. Acupuncture and meditation for military veterans: first steps of quality management and future program development. J Altern Complement Med. 2014;20(9):703-709. doi: 10.1089/acm.2014.0075. PMID: 25119464.
18. Yang M, Baser RE, Liou KT, Li SQ, Piulson L, Panageas KS, Mao JJ. Effect of acupuncture versus usual care on sleep quality in cancer survivors with chronic pain: Secondary analysis of a randomized clinical trial. JAMA Oncol. 2023;9(1):25-34. doi: 10.1001/jamaoncol.2022.5111. PMID: 36420915.
19. Fabbri M, Beracci A, Martoni M, Meneo D, Tonetti L, Natale V. Measuring subjective sleep quality: a review. Sleep Med Rev. 2021;56:101414. doi: 10.1016/j.smrv.2020.101414. PMID: 32544589.
20. Liu F, You J, Li Q, Fang T, Chen M, Tang N, Yan X. Acupuncture for chronic pain-related insomnia: a systematic review and meta-analysis. J Pain Res. 2019;12:397-410. doi: 10.2147/JPR.S192268. PMID: 30787601.



Calum Haycock

My name is Calum and I am a second-year medical student at the University of Plymouth. My current interests in medicine include gastroenterology, nutrition and surgery. This article was part of a healthcare SSU I completed in first year. I enjoy playing for the medics' rugby team and going to the gym. Going forward, I hope to contribute to further research during my career to add to my first publication.

Review

The impact of COVID-19 on neutrophil NETosis and NET-induced immuno-thrombosis

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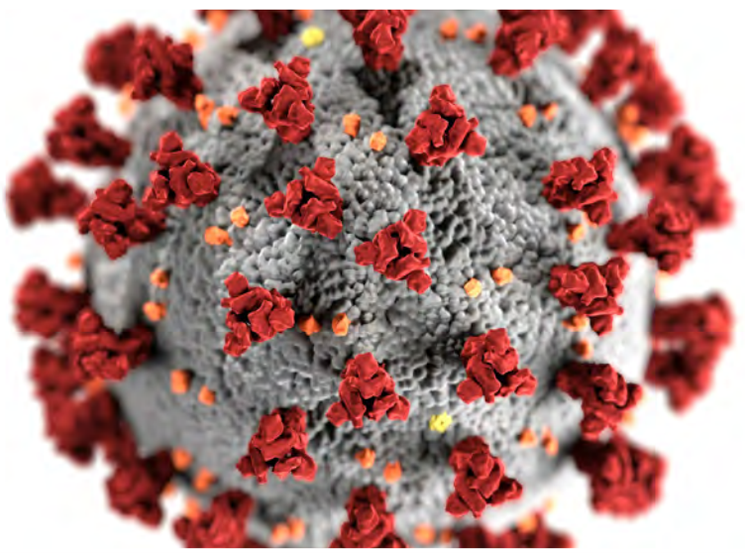

Abstract

Coronavirus disease 2019 (COVID-19), a global health concern, is a severe virus-induced respiratory disease that could progress onto acute respiratory distress syndrome and isolated thrombosis. Excessive neutrophils in the blood of COVID-19 patients have drawn significant attention. This review aims to explore the relationship between elevated neutrophil NETosis and COVID-19 disease severity. Additionally, there is a focus on how NET-induced immuno-thrombosis in COVID-19 leads to thrombotic complications. The literature required to accomplish this was acquired using online databases such as PubMed. Research found elevated serum markers associated with neutrophil NETosis capable of inducing lung tissue damage by apoptosis, including citrullinated histone H3, neutrophil elastase (NE) and myeloperoxidase (MPO) in COVID-19 patients. Studies have shown the virus inducing neutrophil, platelet and complement activation, leading to the production of NETs that release MPO, NE and inhibit anti-thrombin 3, which ultimately progresses to thrombosis. Furthermore, COVID-19 plasma was able to trigger NET formation. Importantly, research shows increased cell-free DNA and MPO-DNA in hospitalised COVID-19 patients on mechanical ventilation compared to patients breathing room air. Therapies targeting dysregulated NETosis via its inhibition and promotion of NET degradation could be beneficial in preventing disease exacerbation.

Abbreviations

ACE – angiotensin-converting enzyme
ARDS – acute respiratory distress syndrome
Cit-H3 – citrullinated-H3
COVID-19 – Coronavirus disease 2019
DNA – deoxyribonucleic acid
MPO – myeloperoxidase
NE – neutrophil elastase
NET – neutrophil extracellular traps
ROS – reactive oxygen species
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
vWF – von Willebrand Factor

Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA enveloped virus.[1] The virus breaches alveolar epithelial membrane by binding to human angiotensin-converting enzyme (ACE) 2 receptor found on lung pneumocytes, epithelial and endothelial cells.[2] To complete fusion, the viral membrane spike protein needs to be cleaved by serine proteases such as TMPRSS2.[3] After spreading rapidly across the globe, COVID-19 was declared a pandemic on 11 March 2020 by the World Health Organization.[4,5] Some typical symptoms of the disease include fever, cough, difficulty breathing and loss of taste, whereas acute respiratory distress syndrome (ARDS) and multiple organ failure are seen more commonly in individuals with severe COVID-19.[6,7] Global deaths attributable to the COVID-19 pandemic are currently exceeding 3.4 million.[8]

Neutrophils account for roughly 70% of circulating human leukocytes.[1] One of their effector mechanisms, NETosis, which utilises NETs (neutrophil extracellular traps) has been suggested as a significant cause of the immunopathological manifestations of the SARS-CoV-2 virus.[6] NETosis is a special form of programmed cell death which is regulated in normal conditions. There are three types of NETosis: suicidal, where the neutrophil ruptures releasing its DNA; vital, where NETs are exocytosed in vesicles; and mitochondrial, where mitochondrial DNA is released as extracellular traps in a

reactive oxygen species (ROS) dependent manner.[9] For a detailed overview of the mechanism of NETosis, refer to **Figure 1**. There are numerous ways in which SARS-CoV-2 virus can induce NETosis which is detailed in **Figure 2**.[6,10-12] Excessive activation of NETs in circulation can also cause hypercoagulability and immuno-thrombosis.[6] Platelet coagulation can occur via two main pathways, namely the intrinsic and extrinsic coagulation pathways (**Figure 3**).[13] Incidence of immuno-thrombosis has been found in 22.7% of critically ill patients with COVID-19 in ICU and 7.9% of non-ICU patients.[14]

There has been an exponential rise in the number of COVID-19 cases worldwide, with no effective treatment. This paper aims to explore the relationship between COVID-19 and NETosis, and to subsequently focus on NET induced immuno-thrombosis.

Methodology

The literature for this review was obtained from PubMed and Google Scholar databases online. Two additional papers were found whilst reviewing reference lists of highly relevant papers which did not appear during initial database searches. Keywords used for theme one were: "neutrophils", "NETosis", "COVID-19" in conjunction with AND to refine the search. Keywords used for theme two were: "neutrophils", "NETosis", "immuno-thrombosis", "COVID-19" in conjunction with "AND" to obtain relevant articles. For both themes synonyms were used with each word using "OR" alongside it to ensure no relevant papers were missed out due to different wording. For example, alternatives for "neutrophils" such as "granulocyte", "polymorphonuclear leukocyte" were used, and "SARS-Cov-2" were used as an alternative to "COVID-19". Furthermore, the truncation symbol "*" was used alongside each word, e.g. "neutrophils*" to ensure no alternatives of each word were missed.

Papers from any country within the last six years were used. This ensured relevance to the rapidly evolving field of COVID-19 and NETosis, reflecting the most current understanding and methodologies. Additionally, this incorporated significant technological advancements in biomedical research, such as improved imaging and advanced data analysis tools. Further resources were found through citations on other papers and clinical reviews. Twenty-four papers and one website were obtained for this review. Refer to **Figure 4** for a full method.

Discussion

Influen e of COVID-19 on NET formation

Serum markers of NETs are elevated in COVID-19 patient sera. These include myeloperoxidase (MPO)-DNA, cell-free DNA and citrullinated-H3 (Cit-H3), which are NETosis-related enzymes capable of inducing lung tissue damage.[4] Thereby we can also infer a rise in neutrophil elastase (NE), which if in a complex with DNA and Cit-H3, could be another serum marker of NETs. This suggests the potential of excessive NETosis in contributing to exacerbation of the disease, perhaps by disrupting alveolar endothelium, promoting lung epithelial apoptosis and degrading alveolar basement membrane.[2,15]

Various studies have demonstrated elevated levels of neutrophil NETosis in individuals with COVID-19.[3,5,16] In one study, blood samples of 16 hospitalised patients with COVID-19 were obtained and their neutrophils were isolated.[5] NET production was then investigated ex vivo by relative fluorescence, which depicted that without stimulation more NETs were produced in the infected cohort compared to their control ($p < 0.0001$). Furthermore, increased levels of NETs were identified in the airways and alveoli of 40% of patients infected with SARS-CoV-2. A limitation of the study is that confounding factors such as diabetes mellitus present within the patient cohort were not mirrored in the control group. This could make the results an overestimation as increased NETosis is observed in individuals with diabetes, hence this may challenge the integrity of results.[17] Similar results were shown in a study on 32 patients with severe COVID-19, demonstrating their plasma NET levels to be elevated using confocal microscopy analysis. In addition, more than 80% of their neutrophils were positive for NETs compared to their control.[3] The study also looked at NET concentration in tracheal aspirate of patients with severe COVID-19 under mechanical ventilation and found a 10-fold increase in plasma concentration. The results may also be influenced by being on mechanical ventilation as it has been found to contribute to an increased level of NET markers in alveoli of critically ill patients.[18] Trauma from mechanical ventilation in lungs may result in the release of damage-associated molecular patterns (DAMPs), leading to neutrophil activation and increased NETosis. Hence, caution is advised in clinical practice when starting ventilation in patients with COVID-19. Perhaps measuring neutrophil count beforehand may allow the risk level of NETosis to be monitored. The study's methodical drawback lies in using qualitative confocal immunofluorescence, hindering quantification without additional techniques such as enzyme-linked immunosorbent assays (ELISA) or flow cytometry. Another prospective cohort study on 28 hospitalised patients with COVID-19 and 5 convalescent patients measured plasma MPO-DNA complexes. They found that survivors of COVID-19 had significantly lower NET levels than non-survivors ($p=0.0004$), suggesting that upon viral clearance NET levels fall.[19]

A study obtained similar results using serum samples from 50 hospitalised patients with COVID-19 comparing their results to 30 healthy controls.[16] They measured three NET markers: MPO-DNA ($p<0.001$), Cit-H3 ($p<0.0001$) and cell-free DNA ($p<0.0001$), with the latter not being specific to NETosis. All three of these markers were elevated in the serum of individuals with COVID-19 compared with controls. Surprisingly, Cit-H3 did not correlate as well as the other two markers and instead correlated strongly with platelet levels ($r=0.45$, $p<0.0001$). This could suggest the existence of multiple pathways to NETosis linked to COVID-19, as peptidyl arginine deiminase-4 (PAD4) is the primary catalyst for Cit-H3 synthesis. An above-mentioned study incubated neutrophils with Cl-Amidine, an inhibitor of PAD4, which showed a reduction in NET production from COVID-19 patient neutrophils.[3] This confirms patients with COVID-19 are more susceptible to PAD-4 dependent NETosis. The PAD4 pathway is only one of the many mechanisms of neutrophil NETosis, such as PAD4 independent, metabolism-mediated etc.[9] On the contrary, in vitro studies have demonstrated some pathways being somewhat non reliant on PAD4 activity.[16] For example, the stimulation of ROS production could be PAD4 independent. Furthermore, neutrophils may undergo cell death through various pathways such as apoptosis and necrosis. Hence, markers such as Cit-H3 may be produced by a type of cell death independent of NETosis as well.

All studies[3,5,16,19] unfortunately have not specified the type of NETosis that they were investigating. This makes finding a therapeutic target for NETosis-induced COVID-19 disease exacerbation challenging, as it is difficult to directly target a specific type of NETosis. However, one study[3] via the inhibition of PAD4 enzyme has shown that PAD4 dependent NETosis is involved in COVID-19, which allows for some targeted therapeutic approaches. Although this area requires more research as there is evidence disputing this claim.

Net induced immuno-thrombosis in COVID-19

Thrombotic complications, including venous, arterial and microvascular thrombosis, are observed in patients with COVID-19.[14] It is defined as immuno-thrombosis, where neutrophils interact directly with platelets and coagulation factors.[19] NETs have been identified as major elements of micro and macro vascular thrombi[20] and in patients with COVID-19, components of NETs, such as cell-free DNA and Cit-H3, can potentially act as coagulation inducers. When NETs are released into circulation, they bind to vessel walls, capturing platelets resulting in blood flow obstruction (**Figure 5**).

An above-mentioned prospective cohort study looked at 16 COVID-19 patient plasma samples for NET formation using confocal microscopy.[19] The study detected significantly higher circulating

platelet-neutrophil aggregates compared to healthy controls (p=0.006). However, they did not observe many thrombotic complications of SARS-Cov-2 in the cohort that other studies have reported on. Additionally, even though they found significantly elevated soluble markers of thrombosis (e.g. Plasma D-dimer and von Willebrand Factor (vWF) antigen levels) in patients with COVID-19 ($p<0.0001$), these did not correlate directly with plasma NET levels within the cohort. This may be due to markers such as vWF being released from activated endothelium early in COVID-19. In the study, the vWF levels measured later may reflect ongoing inflammation.[19] Another reason for the discrepancy may be because D-dimers result from active fibrinolysis, however, NET-rich clots are protected from fibrinolytic breakdown by tissue plasminogen activator. Therefore, this lack of correlation could be due to inhibited thrombus degradation in patients with COVID-19.

In contrast, a study on 36 patients with COVID-19 and 31 healthy controls found that there were significantly higher MPO-DNA complexes and Cit-H3 in COVID-19 patients with thrombotic events compared to those without.[21] In this study COVID-19 patients mainly had mild disease progression, however, they still found strong platelet and neutrophil activation, depicting that the virus itself triggers neutrophil modifications. Surprisingly, the study also found that NET biomarkers did not decrease to normal levels after COVID-19 recovery. This could suggest a degree of neutrophil activation persisting even after recovery.[22] Similar results were found in a study conducted on 44 patients with COVID-19 where cell-free DNA ($p<0.001$), MPO-DNA ($p<0.05$) and cit-H3 ($p<0.01$) were significantly raised in COVID-19 patients in their thrombosis group.[23] A limitation of this study was the use of discarded specimens at various sampling points rather than samples drawn up specifically for research purposes. This leads to the possibility of NETs being partially degraded over time, lowering their measurements, giving underestimates.

During mild SARS-CoV-2, physiological immuno-thrombosis is developed, which is controlled by homeostatic mechanisms as opposed to in severe infections where it is uncontrolled leading to pathological immuno-thrombosis.[24] A case-controlled study showed that both the activation of neutrophils and complement were associated with inducing thrombosis in patients with COVID-19.[25] Complement activation is a biochemical process that enhances immune responses against pathogens by producing proteins such as C3. Findings were confirmed by confocal immunofluorescence microscopy in neutrophils collected from four patients with severe COVID-19, where spontaneous NET formation expressing tissue factor (TF) was observed.[25] When C3 activation was blocked using Cp40, TF expression in control neutrophils was significantly decreased ($p < 0.05$). This indicates C3 inhibition disrupts TF release as a result of NETosis. A limitation of this study is the specificity regarding the use of confocal immunofluorescence. This technique cannot distinguish between NETs, other extracellular structures and debris present in samples, requiring additional validation of results. Furthermore, the study has not considered the likelihood of active fibrinolysis, which is the breakdown of clots, occurring simultaneously with thrombosis within the human body. This can obscure the true extent of clot formation caused by neutrophil and complement activation. Therefore, the study has found the true extent of clot formation whilst the body's response would be lower, making the results of this study an overestimation.

Conclusion

To conclude, studies show increased NETosis in COVID-19 patient plasma highlighting its influence on exacerbating the disease. Alarmingly, critically ill COVID-19 patients being on mechanical ventilation have been shown to increase NETosis, which can further accentuate disease progression. More studies specifically looking at the mechanism of how mechanical ventilation induced NETosis are required, perhaps by measuring DAMPs, such as MPO-DNA in patient serum, investigating its correlation to NET release.

Studies have shown components of NETs and NETosis itself to increase micro and macro vascular thrombi in blood vessels of COVID-19 patients. The virus, by activation of the complement system and platelet activation induced NETosis, leads to immuno-thrombosis. These studies have used confocal immunofluorescence for imaging which is qualitative and nonspecific; hence, future studies should use ELISA or flow cytometry to quantify results and facilitate statistical analysis. Additionally, some studies have not accounted for confounding factors such as the presence of active fibrinolysis. Therefore, in future studies researchers need to measure and control fibrinolytic activity by assessing levels of fibrinolytic markers such as plasminogen or D-dimer and factor these findings into their analysis. Finally, it is integral that studies specify the type of NETosis that they observe in COVID-19 patients along with which NET-related markers correlate more with each type of NETosis.

References

1. Gillot C, Favresse J, Mullier F, Lecompte T, Dogne J-M, Douxfils J. NETosis and the immune system in COVID-19: mechanisms and potential treatments. Frontiers in Pharmacology. 2021;12:708302.
2. Keane C, Coalter M, Martin-Loeches I. Immune system disequilibrium—Neutrophils, their extracellular traps, and COVID-19-induced sepsis. Frontiers in Medicine. 2021;8:711397.
3. Veras FP, Pontelli MC, Silva CM, Toller-Kawahisa JE, de Lima M, Nascimento DC, et al. SARS-CoV-2–triggered neutrophil extracellular traps mediate COVID-19 pathology. Journal of Experimental Medicine. 2020;217(12):e20201129.
4. Borges L, Pithon-Curi TC, Curi R, Hatanaka E. COVID-19 and neutrophils: the relationship between hyperinflammation and neutrophil extracellular traps. Mediators of inflammation. 2020;2020.
5. Masso-Silva JA, Moshensky A, Lam MT, Odish M, Patel A, Xu L, et al. Increased peripheral blood neutrophil activation phenotypes and NETosis in critically ill COVID-19 patients. medRxiv. 2021:2021.01. 14.21249831.
6. Zhu Y, Chen X, Liu X. NETosis and neutrophil extracellular traps in COVID-19: immunothrombosis and beyond. Frontiers in Immunology. 2022;13:838011.
7. Zhang R, Sun C, Han Y, Huang L, Sheng H, Wang J, et al. Neutrophil autophagy and NETosis in COVID-19: perspectives. Autophagy. 2023;19(3):758-67.
8. Organization WH. Global excess deaths associated with COVID-19 (modelled estimates) [Internet] 2023 [cited 2024 May 15] Available from: https://www.who.int/data/stories/the-true-death-toll-of-covid-19-estimating-global-excess-mortality.
9. Tan C, Aziz M, Wang P. The vitals of NETs. J Leukoc Biol. 2021;110(4):797-808.
10. Liao T-L, Liu H-J, Chen D-Y, Tang K-T, Chen Y-M, Liu P-Y. SARS-CoV-2 primed platelets–derived microRNAs enhance NETs formation by extracellular vesicle transmission and TLR7/8 activation. Cell Communication and Signaling. 2023;21(1):304.
11. Hsieh K-H, Chao C-H, Cheng Y-L, Lai Y-C, Chuang Y-C, Wang J-R, et al. Enhancement of NETosis by ACE2-cross-reactive anti-SARS-CoV-2 RBD antibodies in patients with COVID-19. Journal of Biomedical Science. 2024;31(1):39.
12. Allen KC, Ramos-Benitez MJ, Teague H, Chertow DS, Strich JR, Warner S. 249. SARS-CoV-2 spike immune complexes induce NETosis in COVID-19. Open Forum Infectious Diseases. 2023;10(Supplement_2).
13. Morris G, Bortolasci CC, Puri BK, Olive L, Marx W, O'Neil A, et al. The pathophysiology of SARS-CoV-2: a suggested model and therapeutic approach. Life Sciences. 2020;258:118166.
14. Shaw RJ, Bradbury C, Abrams ST, Wang G, Toh CH. COVID-19 and immunothrombosis: emerging understanding and clinical management. British Journal of Haematology. 2021;194(3):518-29.
15. Wang J, Li Q, Yin Y, Zhang Y, Cao Y, Lin X, et al. Excessive neutrophils and neutrophil extracellular traps in COVID-19. Frontiers in Immunology. 2020;11:2063.
16. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI insight. 2020;5(11).
17. Njeim R, Azar WS, Fares AH, Azar ST, Kfoury Kassouf H, Eid AA. NETosis contributes to the pathogenesis of diabetes and its complications. J Mol Endocrinol. 2020;65(4):R65-r76.

18. Mikacenic C, Moore R, Dmyterko V, West TE, Altemeier WA, Liles WC, et al. Neutrophil extracellular traps (NETs) are increased in the alveolar spaces of patients with ventilator-associated pneumonia. Crit Care. 2018;22(1):358.
19. Middleton EA, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood. 2020;136(10):1169-79.
20. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, da Silva LFF, de Oliveira EP, Saldiva PHN, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020;18(6):1517-9.
21. Petito E, Falcinelli E, Paliani U, Cesari E, Vaudo G, Sebastiano M, et al. Association of Neutrophil Activation, More Than Platelet Activation, With Thrombotic Complications in Coronavirus Disease 2019. J Infect Dis. 2021;223(6):933-44.
22. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. Jama. 2020;324(6):603-5.
23. Zuo Y, Zuo M, Yalavarthi S, Gockman K, Madison JA, Shi H, et al. Neutrophil extracellular traps and thrombosis in COVID-19. J Thromb Thrombolysis. 2021;51(2):446-53.
24. Al-Kuraishy HM, Al-Gareeb AI, Al-Hussaniy HA, Al-Harcan NAH, Alexiou A, Batiha GE-S. Neutrophil Extracellular Traps (NETs) and Covid-19: A new frontiers for therapeutic modality. International Immunopharmacology. 2022;104:108516.
25. Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest. 2020;130(11):6151-7.

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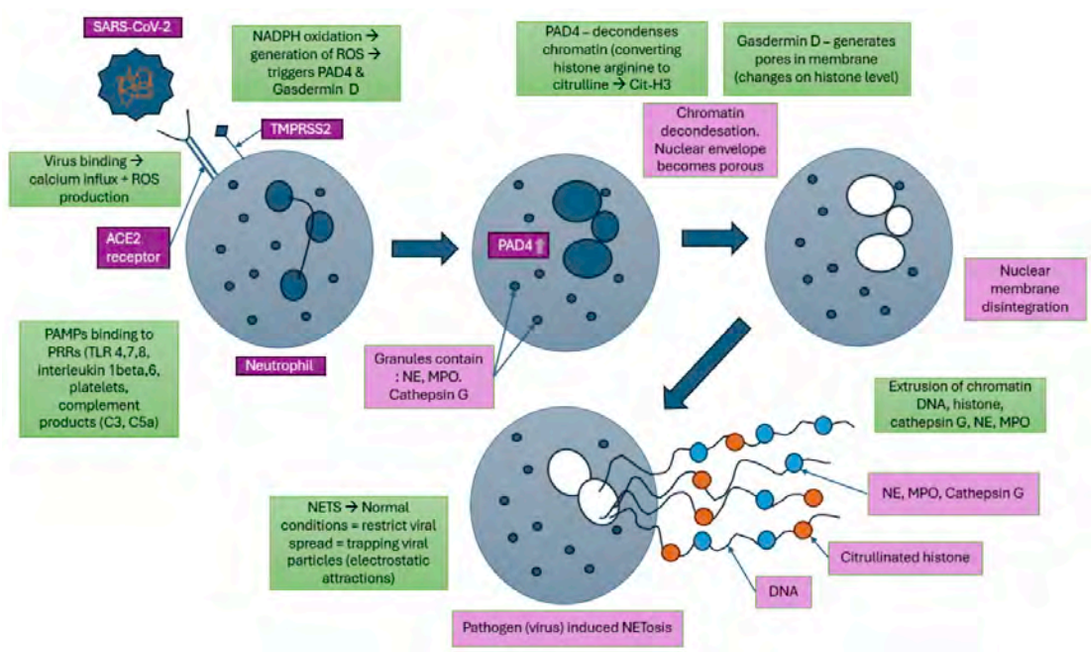

Figure 1. Mechanism of neutrophil NETosis in COVID-19

NETosis is the formation of Neutrophil Extracellular traps during cell apoptosis. It involves the extrusion of chromatin DNA, histones, and antimicrobial proteins into the extracellular space to restrict viral spread.

Created from information in Gillot et al[1], Keane et al[2], Borges et al[4], Zhu et al[6], Al-Kuraishy et al[24]. (No graphical elements from the above papers were used.)

Abbreviations - SARS-COV-2: Severe acute respiratory syndrome coronavirus 2, ACE 2: Angiotensin-converting enzyme 2, TMPSS2: Transmembrane serine protease 2, NADPH: Nicotinamide adenine dinucleotide phosphate, ROS: Reactive Oxygen species, PAD4: Peptidyl arginine deiminase 4, Cit-H3: Citrullinated histone H3, NE: Neutrophil elastase, MPO: Myeloperoxidase, PAMPs: Pathogen associated molecular patterns, PRR: Pattern recognition receptors, TLR: Toll-like receptors, DNA: Deoxyribonucleic acid.

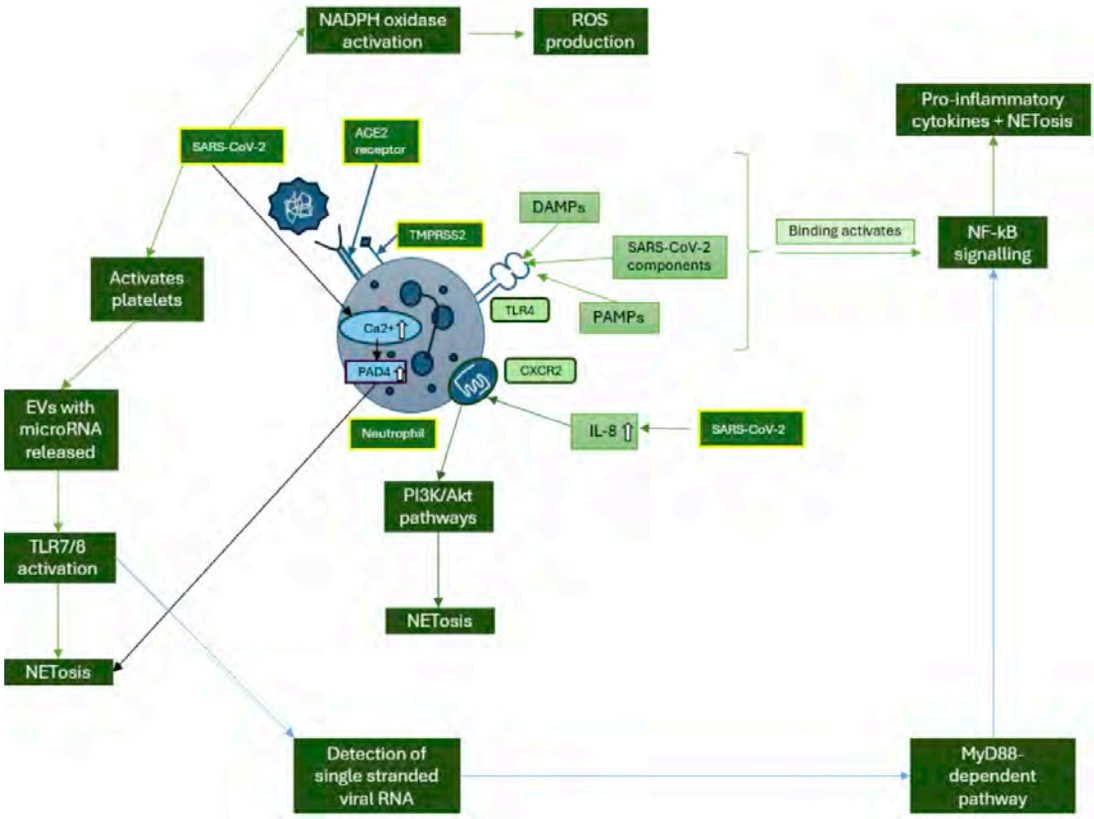

Figure 2. Mechanism of SARS-CoV-2 inducing neutrophil NETosis
Created based on text in Zhu et al[6], Liao et al[10], Hsieh et al[11] and Allen[12]. (No graphical elements from the above papers were used.)
Abbreviations - SARS-COV-2: Severe acute respiratory syndrome coronavirus 2, ACE 2: Angiotensin-converting enzyme 2, TMPSS2: Transmembrane serine protease 2, NADPH: Nicotinamide adenine dinucleotide phosphate, ROS: Reactive Oxygen species, PAD4: Peptidyl arginine deiminase 4, DAMPs: Damage associated molecular patterns, PAMPs: Pathogen associated molecular patterns, TLR: Toll-like receptors, EVs: Extracellular vesicles, microRNA: micro ribonucleic acid, MyD88: myeloid differentiation primary response 88, IL-8: Interleukin 8, CXCR2: C-X-C Motif chemokine receptor 2, PI3K: Phophatidylinositol-4,5-bisphosphate 3-kinase, Akt: protein kinase B, NF-kB: Nuclear factor kappa B.

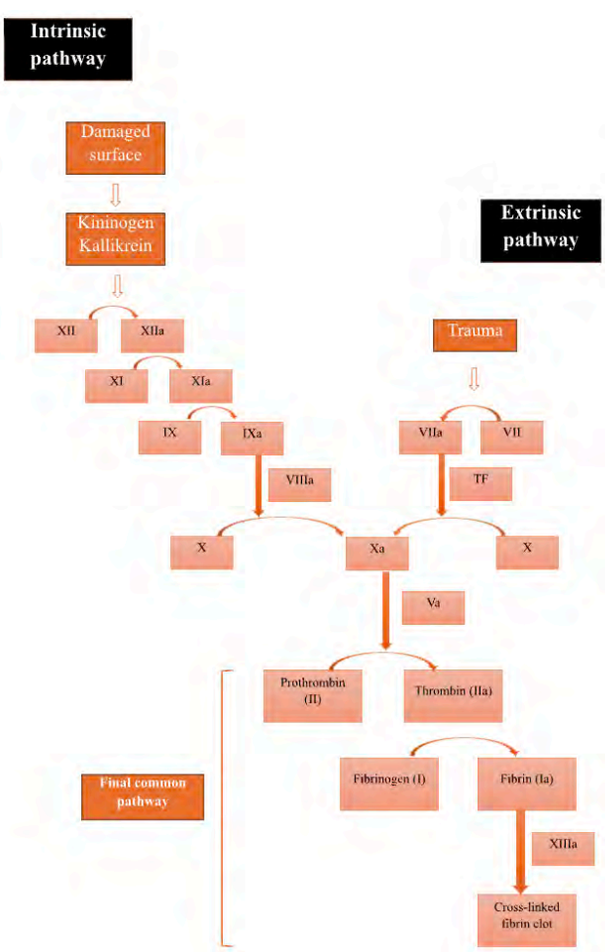

Figure 3. Intrinsic and extrinsic coagulation pathways
Roman numerals represent coagulation factors.
Figure created using data from Morris et al1[3]. (No graphical elements from the above paper was used.)

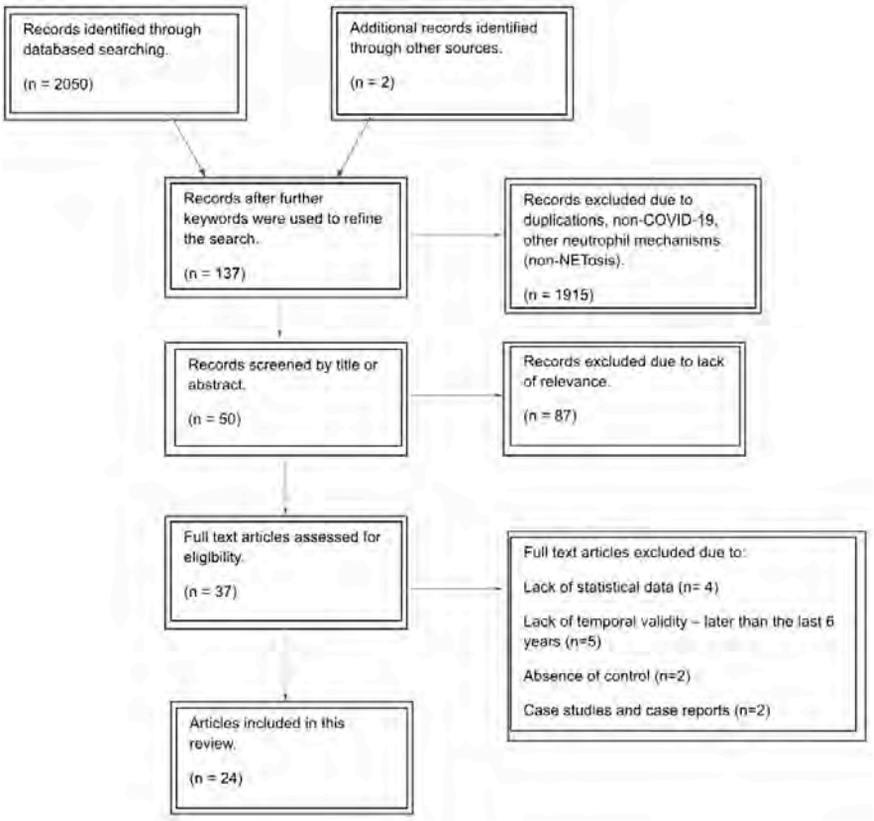

Figure 4. PRISMA diagram depicting the full method.

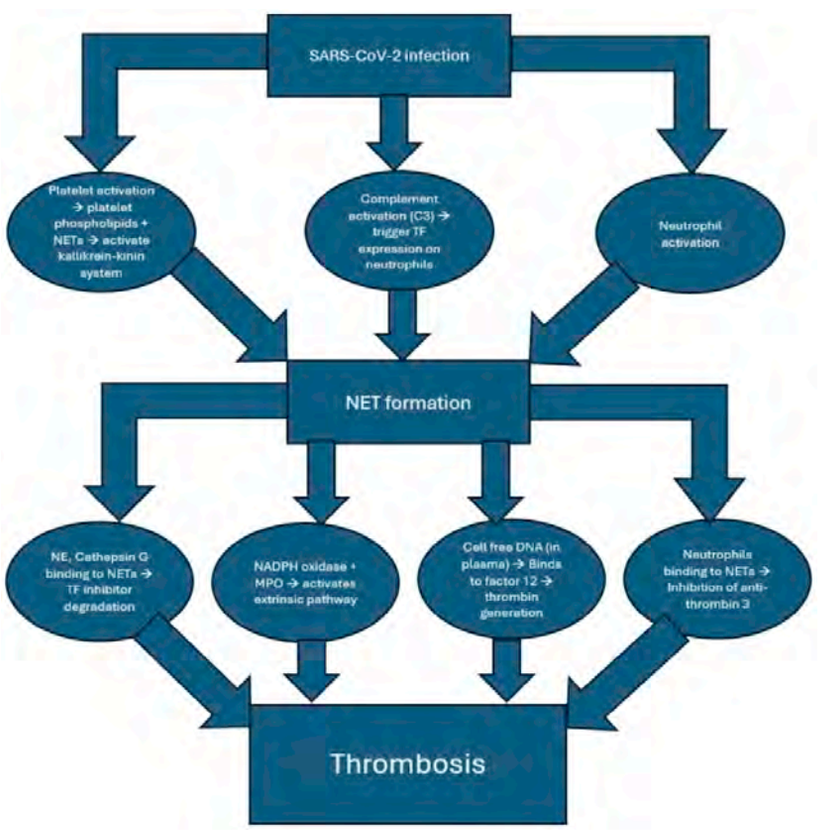

Figure 5. Summary of NETosis and coagulopathy in COVID-19
Created based on information in Zhu et al[6], Al-Kuraishy et al[24]. (No graphical elements from the above papers were used.)
Abbreviations - SARS-COV-2: Severe acute respiratory syndrome coronavirus 2, NETs: Neutrophil extracellular traps, NADPH: Nicotinamide adenine dinucleotide phosphate, NE: Neutrophil elastase, MPO: Myeloperoxidase, TF: Tissue factor, DNA: Deoxyribonucleic acid.

Review

A double-edged sword: discussing the value and pitfalls of chemotherapy in cancer treatment, a review of current research

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Abstract

As one of the leading causes of death worldwide, research into new therapeutic cancer treatments has been at the forefront of medical study for several years. Yet chemotherapy remains the gold-standard treatment. Thus, its continued implementation and efficacy are important to consider. This review will discuss these aspects further. The author concludes that chemotherapy has both negative and positive value. Prescription is dependent on grade, stage and type of cancer, with some having greater benefit than others. More research is needed to address the issues of developing resistance and senescence, as well as a greater focus on chemotherapeutic use in metastatic disease. This research was accomplished by searching the term 'chemotherapy' on peer-reviewed journal databases for seminal reviews. This led to key terms for further research; 'senescence,' and 'cancer resistance.' Studies were excluded if interventional data was not described in detail. Larger sample sizes were considered before smaller sample studies.

Abbreviations

ATP – Adenosine Triphosphate
BAK – Homologous antagonist/killer protein
BAX – Apoptosis regulator protein
BIM – Bcl-2 interacting mediator of cell death
BCL – B-cell lymphoma
CAF – Cancer associated fibroblasts
CSC – Cancer stem cell
CT – Chemotherapy
AT – Adjuvant chemotherapy
ICT – Induction chemotherapy
NAT – Neoadjuvant chemotherapy
PCT – Palliative chemotherapy
DAMPs – Damage associated molecular pathways
EMT – Epithelial-mesenchymal transition
HMGB1 – High mobility group box 1
IFNy – Interferon gamma
IL-(number) – Interleukin (number)
MHC – Major histocompatibility complex
MMP – matrix metalloproteinase
NF-kB – Nuclear factor-kB
PDGF – Platelet derived growth factor
QOL – Quality of life
ROS – Reactive oxygen species
SASP – senescence-associated secretory phenotype
STAT3 – Signal transducer and activator of transcription 3
TME – Tumour Microenvironment
TNFSF4 – Tumour necrosis factor superfamily 4
VEGF – Vascular endothelial growth factor

Introduction

Cancer involves the growth of abnormal cells within the body. With primary cancer, cells remain within the initial seeded organ creating a tumour. On the contrary, secondary cancer involves cells spreading beyond the initial organ via haematogenous, lymphatic or direct invasion; this process is known as the metastatic cascade. Local invasion allows intravasation of cancer cell aggregates into the circulatory system. After survival and subsequent adherence to the endothelial lining of the vasculature, these cells extravasate forming

micrometastasis which colonise to form macroscopic metastases.[1] This metastasis is limited according to primary tumour environment, summed up by the seed and soil hypothesis: metastasis depends on crosstalk between cancer cells (the 'seeds') and organ tissue tropism (the 'soil').[2]

Once seeded, cancer cells proliferate to become highly heterogenous. Their contents are termed the tumour microenvironment (TME). These include tumour educated macrophages/neutrophils, cancer associated fibroblasts (CAFs) and disordered vasculature, all held within a modified extracellular matrix. These contents allow the TME to produce substances like vascular endothelial growth actor (VEGF), platelet derived growth factor (PDGF), and interleukin-10 (IL-10), which promote angiogenesis and immune suppression, encouraging disease dissemination[3]

Chemotherapy (CT) is a cytotoxic therapy that non-selectively targets proliferating cancer cells. It is prescribed in one of four ways: induction (ICT), neoadjuvant (NAT), adjuvant (AT) and palliative (PCT) CT therapies. The difference between these therapies is timing. ICT describes CT as the primary treatment, used to achieve rapid tumour control. NAT involves shrinking the tumour prior to other treatments, whilst AT involves eliminating left over circulating tumour cells after primary treatment. PCT is used to improve quality of life through symptomatic control – it has no curative intent.

CT is prescribed across a variety of cancer types like lymphoma, breast and rectal.[4] Various drug classes have been synthesised with different biochemical modalities. These include alkylating agents, antimetabolites, antimicrotubule agents and topoisomerase inhibitors (anthracyclines). Each drug class targets a different part of the cell cycle: Alkylating agents destabilise DNA; antimetabolites compete for/substitute key DNA metabolites; and anthracyclines/topoisomerases inhibit enzymes involving DNA uncoiling.[5-6] As such, polychemotherapy is often used to maximise treatment targets. CAPOX is one example which utilises oxaliplatin and capecitabine in the treatment of gastrointestinal cancers.[7] This review will discuss the value of CT as a treatment modality, as well as the issues associated with its use.

Methodology

This research was accomplished by searching on journal databases like PubMed, Elsevier, and Google Scholar using the term 'chemotherapy'. Revision of seminal reviews led to key terms for further research; 'senescence,' and 'cancer resistance.' Only peer-reviewed work published in English was included. Studies were excluded if their focus was outside the scope of the review or if the interventional treatment was not overtly described. All other studies were critically appraised using the 10-step guide produced by Young and Solomon.[8]

Therapy in four forms

Each of the four forms of CT have differing benefits and issues associated with their prescription. One benefit that applies to all four types of therapy is that it is non-selective: able to target different cells of the TME. By causing stress and apoptotic death to the cells, damage-associated molecular patterns (DAMPs) are released in the order of calreticulin, adenosine triphosphate (ATP) and high mobility group box 1 (HMGB1). They interact with corresponding receptors on dendritic cells to allow tumour antigen presentation with subsequent T-cell response. Anthracyclines are particularly effective in allowing calreticulin translocation, but this process of immunogenic cell death can be induced by Bleomycin, Gemcitabine, and Cyclophosphamide.[5,9-10] This is particularly effective for cancers like acute myeloid leukaemia, with 60–85% of adults <60yrs achieving remission status after initial treatment.[11]

However, as dying tumour cells release cell-free chromatin, they also induce apoptosis and inflammation in phenotypically normal cells, leading to undesirable side effects.[12] Tumour lysis syndrome – a life-threatening complication of cancer treatment – is associated with an in-hospital mortality of 21%.[13-14] Other side effects like mucositis and nausea/vomiting can be poorly tolerated, leading to early CT cessation. A study found that of 229 patients receiving CT for early breast cancer, 24% had early cessation of the therapy due to unwanted side effects. A further 18% and 27% had dose reductions and delays respectively, with lethal toxicity occurring in 38%. It is important to note that the retrospective and non-randomised nature of this cohort study limit the integrity of these results.[15] Even so, this highlights how side effects from CT can potentially limit a patient's quality of life (QOL).

Regarding ICT, certain cancers respond particularly well due to their highly proliferative and heterogenous nature. A case review reported that out of 25 patients with choriocarcinoma, 17 had complete recovery after chemotherapy.[16] A phase II trial similarly demonstrated that 85% of 197 patients with acute lymphoblastic leukaemia had complete remission for 29 months on a 5-drug regime containing cyclophosphamide, daunorubicin, vincristine, prednisone and L-asparaginase.[17] Though not beneficial in every malignancy, they are an appropriate primary treatment in highly proliferative and/or system wide cancers such as leukaemia and lymphoma.

When CT is not an appropriate primary treatment, NAT can be used prior to any surgical approaches. This would be indicated in cancers with a solid malignancy, such as breast or lung adenocarcinoma. The BrighTNess randomised control trial (RCT) reported that out of 141 stage II/III triple negative breast cancer patients deemed ineligible for conservation surgery, 75 were deemed eligible after NAT. This equates to 53.2%.[18] Furthermore, a separate study indicated that NAT lowered positive margins from 21.8 to 15.5% in pancreatic head adenocarcinoma ($p<0.0001$). This indicates a promotion of better survival outcomes as positive margins are associated with poorer survival (HR 1.702 $p<0.0001$).[19] As such, NAT is an appropriate treatment when surgical resection is the primary method of care. Other purported rationales for NAT include response assessment to treatment allowing early cessation when deemed ineffective and an improvement in patient survival.[20] One study found that initiation of NAT was associated with a reduction in disease recurrence (HR: 0.73, P=0.003) and mortality (HR: 0.67, P <0.001) when compared with surgery alone. This also included disease-free survival (73.1% vs 64.5%) and 5-year overall survival (79.9% vs 72.6%).[21]

Before the development of NAT, AT was the predominate form of CT, usually prescribed after surgical resection of a tumour to decrease the likelihood of disease recurrence. This has been proven by several different studies. The LACE collaborative group showed an absolute 5-year benefit of 5.4% from the use of Cisplatin AT in non-small cell lung cancer, with benefits dependant on disease staging (1A: HR=1.40, 1B: HR=0.93, II: HR=0.83 etc.)[22] Data analysis from 2000–2009 has similarly shown that cancer mortality has declined by 13.8% with AT drug innovation (8%).[23] An important point to note is that, as the name suggest, AT is used alongside other therapies. It can further be combined with NAT to increase survival, with one study 6.3% increase in survival (p=0.005) of individuals with rectal cancer, compared to those who did not receive both.[24]

What of PCT? A meta-analysis of 11 trials evaluating first-line CT treatment durations in metastatic breast cancer showed statistically significant differences in respect to shorter and longer durations. This was between hazard ratios (0.91, P=0.46) of overall survival and progression free survival (0.64, P= <0.001).[25] The longer treatment lasted, the better the outcome for metastatic disease. Nonetheless, would this simply prolong the inevitable rather than improve QOL? A review of 13 studies by Akhlaghi et al noted that QOL was reduced when PCT was prescribed. Prolonged hospitalisation, invasive ventilation, and death in non-preferred environments were significantly more likely in patients continuing with PCT at end of life. QOL was increased when other needs like mental health, spiritual beliefs and management of symptoms were addressed.[26] One

could argue then that these aspects of care (usually addressed by a specialist palliative care team) are of greater significance to QOL than PCT.

The crux of the issue: developing resistance

One pitfall of CT to consider is treatment resistance. This can occur through the promotion of epithelial-mesenchymal transition (EMT), a process that involves cancerous epithelial cells gaining mesenchymal phenotypes through dissociation with E-cadherin protein. CT can upregulate Snail and Twist transcription factors that lower E-cadherin transcription, promoting further EMT through weakening cell adhesion, thus leading to greater potential for metastasis.[27-28]

Snail and Twist can further affect anti and pro apoptotic protein ratios like BCL-2: BAX, leading to resistance and proliferation via drug target alteration.[29-30] This is particularly detrimental to epithelial-based cancers. One study involving advanced melanoma showed an increase in overall survival rate of 72.9% with a 95% confidence interval when using immunotherapy drug Nivolumab versus 42.1% using CT dacarbazine. Progression free survival was 5.1 months for nivolumab versus 2.2 for dacarbazine with a P value of P<0.001.[31]

The process of anoikis refers to cells which undergo programmed cell death due to detachment from the extracellular matrix. Resistance to this process occurs through overactivation of Src tyrosine kinase (which is upregulated in cancer cells) by reactive oxygen species (ROS). This then leads to BIM protein degradation.[30] BIM forms one of the pro-apoptotic members of the BCL2 family which allow the initiation of apoptosis. When degraded, it can no longer bind to the anti-apoptotic proteins of the same family (BCL2, BCLX etc), causing their levels to become elevated. This inhibits the effector pro-apoptotic proteins (Bax and Bak) from initiating apoptosis. Thus, uncontrolled growth of abnormal cells is promoted.[32] CT promotes anoikis resistance by directly increasing the amount of ROS within the body. Drug classes like the anthracyclines, topoisomerase inhibitors and alkylating agents are all believed to produce the highest number of ROS.[33-34]

ROS can also cause non-specific DNA mutation in non-aberrant healthy cells. Any damage to regulatory genes on these can increase oncogene expression rate, allowing subsequent malignant transformation.[35] Coupled with altered apoptosis, this can lead to an upsurge in metastatic potential.

Senescence

Metastatic potential can be increased by CT through the mobilisation of inflammatory mediators and cancer stem cells (CSCs). Prostaglandin E2 is found in many cancers i.e. colon, lung and breast. When it is secreted by CT-induced dying cells, it promotes CSC proliferation.[5] CSCs have a naturally quiescent nature alongside apoptotic resistance and strong DNA repair abilities. The reliance on cell proliferation by CT means that they are more inherently resistant, able to escape destruction.[33] Having strong damage response mechanisms like nucleotide excision and homologous recombination also allow the potential reversal of drug induced damage; these both would allow reversal of platinum-based drug damage.[30]

CAFs (derived from CSCs), secrete matrix metalloproteinase 3 (MMP) which degrades E-cadherin and promotes EMT.[36] They also limit apoptosis and confer resistance, demonstrated in a study using increased gene tumour necrosis factor superfamily 4 (TNFSF4). This gene had a positive correlation with increased lung adenocarcinoma tumour size after CT with cisplatin. It also had increased expression by the CAFs after CT (n=58 p<0.0001) and was demonstrated to inhibit apoptosis and promote chemoresistance by activating the NF-kb /BCL-XL pathway. It is important to note that research into the role of TNFSF4 in tumour cells is some of the first of its kind. It must be approached with a level of optimistic caution until further peer review.[37]

Furthermore, not every cell is destroyed by CT. Those that remain can instead become senescent. This is a natural consequence of CT due to the induction of DNA double-stranded breaks stopping cell proliferation.[12,35,38] These senescent cells express inflammatory genes that are activated by NF-kB transcription factor allowing the production of several senescence-associated secretory phenotype (SASP) molecules. Examples include IL-1, IL-6, MMP-1 and MMP-3.[36] CT drugs like Cisplatin, 5-Fluorouracil and Mitomycin-C among others induce NF-kB, thus increasing chronic inflammation in the TME.[35] This was demonstrated using doxorubicin. Dermal fibroblasts exposed to 250nM doxorubicin showed a sharp increase in senescence-associated B-galactose indicating increased senescent cell presence, alongside DNA damage from measured 53BP1 foci.[39] Though an initial stopgap for immediate cell proliferation in primary cancer, their accumulation alongside oncogene reprogramming from DNA damage can lead to tumorigenesis through the addition of CSC-like phenotypes.[40] Pharmacological research in other cancer therapies specially aimed at reducing senescence could help mediate chemoresistance.

CT drugs like Paclitaxel and Cyclophosphamide can also cause the production of IL-6, one of the SASP molecules. This cytokine increases M2 macrophages levels which are involved with wound healing and cell proliferation. Furthermore, IL-6 is a potent immunosuppressant in the TME; it inhibits dendritic cells and induces T-regulatory cells (T-reg).[35] One study regarding melanoma interestingly showed that low dose (1–2.5mg per mouse) cyclophosphamide reduced T-reg numbers even with increased IL-6. This however did not allow for greater survival. It also downregulated perforin concentration in cytotoxic T-cells diminishing their function (P<0.05). Most importantly, it promoted the accumulation of inflammatory factors like IL-5 and Interferon gamma (IFNy) (P <0.01) with cyclophosphamide treated mice over untreated same tumour-bearing mice.[40] This increase in inflammation coupled with senescence and the process of immunoediting could explain the similar levels of survival between groups, thus painting CT as a poor adjunct in low dosages.

Combination therapy

What then is immunoediting and what is its significance? Immunoediting is a response of the immune system that involves three phases: elimination, equilibrium and escape. The immune system detects highly immunogenic cancer cells via restricted major histocompatibility complex II (MHC-II) antigen presentation to helper T cells. Cytotoxic T cells then quickly destroy these cancer cells via perforin-1/granzyme B, fas-ligand associated apoptosis and/or IFNy release. Natural Killer T cell activation occurs and protects against further metastasis of antigenically identical cells. However, more weakly immunogenic cells can escape detection and proliferate further, gaining more chemo-resistant and aggressive phenotypes.[10,41] Tumours undergoing this process are described as 'cold,' and difficult to treat with CT. How then can we transform them into immunogenically 'hot' tumours?

Immunotherapy in combination with CT is showing promise amongst current literature. Studies reviewed by Salas-Benito have shown that pembrolizumab (a PD-1 inhibitor) combined with CT increased overall survival (HR 0.49; P <0.001) in non-small cell lung adenocarcinoma and squamous carcinoma (HR 0.64; P <0.001). Early-stage triple negative breast cancer treated with Pembrolizumab and CT also noted a complete response rate of 64.8% versus 51.2% with monotherapy CT, a difference of 13.6% (P<0.001).[42] Even so, immunotherapy has challenges that need addressed. Therapy-related toxicities and 'on target, off tumour' responses leading to treatment failure are just some.[43] Further research into this topic is outside the scope of this review but certainly worth considering.

Final thoughts

The rationale behind CT treatment in cancer is undeniable. With ICT, it has been proven to be relatively effective in highly proliferative

cancers. NAT also helps to improve survival outcomes through lowering positive margins and allowing greater patient inclusion in conservative surgery. AT has been used to help stop the reoccurrence of disease after primary treatment. As new drugs and treatments are discovered, more research is needed to see how AT (and NAT) fit in with this ever-changing oncological landscape. However, metastatic disease still eludes modern science. The actual processes behind how metastasis occur are only now beginning to be understood. Without this basic knowledge, PCT is yet to be used to the fullest. Currently, it remains to improve QOL in end-of-life care, which even then, research suggests is better done via other means – improving mental health etc. PCT is currently not used in a curative fashion but with greater research, one day it could be.

References

1. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. (2020) Molecular principles of metastasis: a hallmark of cancer revisited, Signal transduction and Targeted Therapy, 5(28), [Online]. Available at: https://doi.org/10.1038/s41392-020-0134-x Accessed: 22 January 2024
2. Fidler IJ. (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited, Nature reviews cancer, 3, pp. 453-458 [Online]. Available at: https://doi.org/10.1038/nrc1098 Accessed: 17 January 2024
3. Anderson NM, Simon MC. (2020) The tumor microenvironment, Cell Press, 30(16), pp. 921-925 [Online]. Available at: https://doi.org/10.1016/j.cub.2020.06.081 Accessed: 27 January 2024
4. Arruebo M, Vilaboa N, Saez-Gutierrez B, Lambea J, Tres A, Valladares M, et al. (2011) Assessment of the evolution of cancer treatment therapies, Cancers, 3(3), pp. 3279-3330 [Online]. Available at: https://doi.org/10.3390/cancers3033279 Accessed: 14 January 2024
5. Tilsed CM, Fisher SA, Nowak AK, Lake RA, Joost Lesterhuis W. (2022) Cancer chemotherapy: insights into cellular and tumor microenvironmental mechanisms of action, Frontiers in Oncology, 12, [Online]. Available at: https://doi.org/10.3389/fonc.2022.960317 Accessed: 16 January 2024
6. Aboud K, Meissner M, Ocen J, Jones R. (2023) Cytotoxic chemotherapy: clinical aspects, Medicine, 51(1), pp. 23-27 [Online]. Available at: https://doi.org/10.1016/j.mpmed.2022.10.005 Accessed: 14 January 2024
7. Cancer Research UK (2024) Cancer drugs A to Z list, Available at: https://www.cancerresearchuk.org/about-cancer/treatment/drugs Accessed: 24 January 2024
8. Young J, Solomon MJ. (2009) How to critically appraise an article, Nature Clinical Practice Gastroenterology & Hepatology, 6(2), pp. 82-91 [Online]. Available at: Accessed: 8 January 2024
9. Hernandez C, Huebener P, Schwabe RF. (2016) Damage-associated molecular patterns in cancer: a double-edged sword, Oncogene, 35, pp. 5931-5941 [Online]. Available at: https://doi.org/10.1038/onc.2016.104 Accessed: 21 January 2024
10. Wang Y-J, Fletcher R, Yu J, Zhang L. (2018) Immunogenic effects of chemotherapy-induced tumor cell death, Genes & Diseases, 5(3), pp. 194-203 [Online]. Available at: https://doi.org/10.1016/j.gendis.2018.05.003 Accessed: 25 January 2024
11. American Cancer society (2019) Cancer treatment & survivorship: Facts & figures 2019-2021, Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf Accessed 30 July 2024
12. Mittra I, Pal K, Pancholi N, Shaikh A, Rane B, Tidke P, et al. (2017) Prevention of chemotherapy toxicity by agents that neutralize or degrade cell-free chromatin, Annals of Oncology, 28(9), pp. 2119-2127 [Online]. Available at: https://doi.org/10.1093/annonc/mdx318 Accessed: 17 January 2024
13. Durani U, Shah ND, Go RS. (2017) In-hospital outcomes of tumor lysis syndrome: a population-based study using the national inpatient sample, The Oncologist, 22(12), pp. 1506-1509 [Online]. Available at: https://doi.org/10.1634/theoncologist.2017-0147 Accessed: 17 January 2024
14. McBride A, Westervelt P. (2012) Recognizing and managing the expanded risk of tumor lysis syndrome in hematologic and solid malignancies, Journal of Hematology & Oncology, 5, [Online]. Available at: https://doi.org/10.1186/1756-8722-5-75 Accessed: 23 February 2024
15. Delgado-Ramos GM, Nasir SS, Wang J, Schwartzberg LS. (2020) Real-world evaluation of effectiveness and tolerance of chemotherapy for early-stage breast cancer in older women, Breast Cancer Research and Treatment, 182, pp. 247-258 [Online]. Available at: https://doi.org/10.1007/s10549-020-05684-5 Accessed: 24 January 2024
16. Yang M, Peng L. (2017) Role of chemotherapy and thrombolysis in treatment of choriocarcinoma accompanied with pulmonary embolism, Medicine, 96(36), [Online]. Available at: https://doi.org/10.1097/MD.0000000000007866 Accessed: 17 January 2024
17. Larson RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P et al. (1995) A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811, Blood, 85(8), pp. 2025-2037 [Online]. Available at: https://pubmed.ncbi.nlm.nih.gov/7718875/ Accessed: 23 February 2024
18. Golshan M, Loibl S, Wong SM, Houber JB, O'Shaughnessy J, Ruho HS et al. (2020) Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer, JAMA Surgery, 155(3), [Online]. Available at: https://doi.org/10.1001/jamasurg.2019.5410 Accessed: 23 January 2024
19. Greco SH, August DA, Shah MM, Chen C, Moore DF, Masanam M et al. (2021) Neoadjuvant therapy is associated with lower margin positivity rates after Pancreaticoduodenectomy in T1 and T2 pancreatic head cancers: an analysis of the National Cancer Database, Surgery Open Science, 3, pp. 22-28 [Online]. Available at: https://doi.org/10.1016/j.sopen.2020.12.001 Accessed: 20 January 2024
20. Masood S. (2016) Neoadjuvant chemotherapy in breast cancers, Women's Health, 12(5), pp. 480-491 [Online]. Available at: https://doi.org/10.1177/1745505716677139 Accessed: 23 February 2024
21. Aliseda A, Arrendondo J, Sánchez-Justicia C, Alvarellos A, Rodríguez A, Matos I et al. (2024) Survival and safety after neoadjuvant chemotherapy or upfront surgery for locally advanced colon cancer: meta-analysis, British Journal of Surgery, 111(2), pp. znae021 [Online]. Available at: https://doi.org/10.1093/bjs/znae021 Accessed: 27 November 2024
22. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepaerd FA, Stephens RJ et al. (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group, Journal of clinical oncology, 26(21), pp.3552-3559 [Online]. Available at: https://doi.org/10.1200/JCO.2007.13.9030 Accessed: 27 November 2024
23. Lichtenberg FR. (2014) Has medical innovation reduced cancer mortality?, CESifo Economic Studies, 60(1), pp. 135-177 [Online]. Available at: https://doi.org/10.1093/cesifo/ift014 Accessed: 22 January 2024
24. Polanco PM, Mokdad AA, Zhu H, Choti MA, Heurta S. (2018) Association of adjuvant chemotherapy with overall survival in patients with rectal cancer and pathologic complete response following neoadjuvant chemotherapy and resection, JAMA Oncology, 4(7), pp. 938-943 [Online]. Available at: https://doi.org/10.1001/jamaoncol.2018.0231 Accessed: 25 January 2024
25. Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, Amadori D et al. (2011) Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials, Journal of Clinical Oncology, 29, [Online]. Available at: https://doi.org/10.1200/JCO.2010.31.5374 Accessed: 26 January 2024
26. Akhlaghi E, Lehto RH, Torabikha M, Nia HS, Taheri A, Zaboli E et al. (2020) Chemotherapy use and quality of life in cancer patients at the end of life: an integrative review, Health Qual Life Outcomes, 18, [Online]. Available at: https://doi.org/10.1186/s12955-020-01580-0 Accessed: 26 September 2024
27. Su J-X, Li S-J, Zhou X-F, Zhang Z-J, Yan Y, Liu S-L, Qi Q. (2023) Chemotherapy-induced metastasis: molecular mechanisms and clinical therapies, Acta Pharmacologica sinica, 4, pp. 1725-1736 [Online]. Available at: https://doi.org/10.1038/s41401-023-01093-8 Accessed: 24 February 2024
28. Dart A. (2023) EMT in chemoresistance, Nature Reviews Cancer, 23, [Online]. Available at: https://doi.org/10.1038/s41568-023-00581-7 Accessed: 25 January 2024
29. Taddei ML, Giannoni E, Fiaschi T, Chiarugi P. (2011) Anoikis: an emerging hallmark in health and diseases, The Journal of Pathology, 226(2), pp. 380-393 [Online]. Available at: https://doi.org/10.1002/path.3000 Accessed: 21 January 2024
30. Hasan S, Taha R, Omri HE. (2018) Current opinions on chemoresistance: an overview, Bioinformation, 14(2), pp. 80-85 [Online]. Available at: https://doi.org/10.6026/97320630014080 Accessed: 25 February 2024
31. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation, The New England Journal of Medicine, 372(4), pp. 320-330 [Online]. Available at: https://doi.org/10.1056/NEJMoa1412082 Accessed: 22 February 2024
32. Koenig MN, Naik E, Rohrbeck L, Herold MJ, Trouson E, Bouillet P et al. (2014) Pro-apoptotic BIM is an essential initiator of physiological endothelial cell death independent of regulation by FOXO3, Cell Death & Differentiation, 21, pp. 1687-1695 [Online]. Available at: https://doi.org/10.1038/cdd.2014.90 Accessed: 27 January 2024
33. Yang H, Villani RH, Wang H, Simpson MJ, Roberts MS, Tang M et al. (2018) The role of cellular reactive oxygen species in cancer chemotherapy, Journal of Experimental & Clinical Cancer Research, 37, [Online]. Available at: https://doi.org/10.1186/s13046-018-0909-x Accessed: 24 January 2024
34. de Freitas Saito R, Rangel MC, Chandler M, Beasock D, Afonin KA, Chammas R. (2023) Cancer therapy-induced inflammation and its consequences, in Ribeiro de Araujo D, Carneiro-Ramos M. (ed.) Biotechnology Applied to Inflammatory Diseases. Interdisciplinary Biotechnological Advances. Singapore: Springer [Online]. Available at: https://doi.org/10.1007/978-981-19-8342-9_4 Accessed: 15 January 2024
35. Behranvand N, Nasri F, Emameh RZ, Khani P, Hosseini A, Garssen J et al. (2021) Chemotherapy: a double-edged sword in cancer treatment, Cancer Immunology, Immunotherapy, 71, pp. 507-526 [Online]. Available at: https://doi.org/10.1007/s00262-021-03013-3 Accessed: 22 January 2024

36. Feng B, Wu J, Shen B, Jiang F, Feng J. (2022) Cancer-associated fibroblasts and resistance to anticancer therapies: status, mechanisms, and countermeasures, Cancer Cell International, 22, [Online]. Available at: https://doi.org/10.1186/s12935-022-02599-7 Accessed: 16 January 2024
37. Li Y, Chen Y, Miao L, Wang Y, Yu M, Yan X et al. (2021) Stress-induced upregulation of TNFSF4 in cancer-associated fibroblast facilitates chemoresistance of lung adenocarcinoma through inhibiting apoptosis of tumor cells', Cancer Letters, 497, pp. 212-220 [Online]. Available at: https://doi.org/10.1016/j.canlet.2020.10.032 Accessed: 16 January 2024
38. Prasanna PG, Citrin DE, Hildesheim J, Ahmed MM, Venkatachalam S, Riscuta G et al. (2021) Therapy-induced senescence: opportunities to improve anticancer therapy, Journal of the National Cancer Institute, 113(10), pp. 1285-1298 [Online]. Available at: https://doi.org/10.1093/jnci/djab064 Accessed: 20 January 2024
39. Demaria M, O'Leary MN, Chang J, Shao L, Liu S, Alimirah F et al. (2017) Cellular senescence promotes adverse effects of chemotherapy and cancer relapse, Cancer Discovery, 7(2), pp. 165-176 [Online]. Available at: https://doi.org/10.1158/2159-8290.CD-16-0241 Accessed: 22 February 2024
40. Sevko A, Sade-Feldman M, Kanterman J, Michels T, Falk CS, Umansky L et al. (2013) Cyclophosphamide promotes chronic inflammation–dependent immunosuppression and prevents antitumor response in melanoma, Journal of Investigative Dermatology, 133(6), pp. 1610-1619 [Online]. Available at: https://doi.org/10.1038/jid.2012.444 Accessed: 17 January 2024
41. Watson LJ. (2023) Immune response, Available at: https://geekymedics.com/immune-response/ Accessed: 21 February 2024
42. Sala-Benito D, Pérez-Gracia JL, Ponz-Sarvisé M, Rodriguez-Ruiz ME, Martínez-Forero I, Castañón E et al. (2021) Paradigms on immunotherapy combinations with chemotherapy, Cancer Discovery, 11(6), pp. 1353-1367 [Online]. Available at: https://doi.org/10.1158/2159-8290.CD-20-1312 Accessed: 27 September 2024
43. Tang L, Huang Z, Mei H, Hu Y. (2023) Immunotherapy in hematological malignancies: achievements, challenges and future prospects, Signal transduction and targeted therapy, 8, [Online]. Available at: https://doi.org/10.1038/s41392-023-01521-5 (Accessed: 27 September 2024

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Hi there! My name is Callista, and I am a third-year graduate medical student at Queen's University Belfast. I am currently interested in the fields of infectious medicine, pathology and cardiology. Specifically, I have a passion for parasitology and how such organisms can affect the body on both a macro and microscopic level. Outside of medicine, I am a keen Dungeons and Dragons (DnD) player, as well as an avid foodie.

Review

The effectiveness of using ulinastatin as a therapeutic agent in the treatment of sepsis

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Abstract

Clinical trials have shown that ulinastatin (UTI), an anti-inflammatory substance, can improve outcomes for sepsis patients.[1-3] The treatment, usually administered intravenously, has been shown to reduce mortality rates[1] and attenuate sepsis-induced inflammation[4] and organ damage.[5] Newer research has attempted to explain the mechanism behind its ability to reduce inflammation by measuring various inflammatory markers.[6,7] Ulinastatin has a role in reducing TNF-α, IL-1 and IL-68 as well as (CRP),[6] TLR-4 and MyD88.[7] These are all released into the bloodstream during inflammation.

This review will explore research from peer-reviewed scientific journals to investigate the effectiveness of using ulinastatin in reducing mortality, inflammation and organ damage in sepsis. It will also explore the change in effectiveness of ulinastatin when combined with other treatments such as glutamine[9,10] or administered differently (e.g. intraintestinally).[9,11]

Abbreviations

ALT – Alanine aminotransferase
ALP – Alkaline phosphatase
CLP – Caecal ligation and puncture
CRP – C-reactive protein
IL – Interleukin
LDH – Lactate dehydrogenase
MAPK – Mitogen-activated protein kinases
MyD88 – Myeloid differentiation primary response 88
PCT – Procalcitonin
TLR – Toll-like receptor
TNF – Tumour necrosis factor
UTI – Ulinastatin
WBC – White blood cell

Introduction

Sepsis is currently defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection".[12] It is an extremely prevalent and deadly condition, with 33.1 million cases reported worldwide in 2017, with an estimated 11 million deaths.[13]

In sepsis, both the pro-inflammatory and anti-inflammatory pathways are upregulated, leading to tissue damage and organ dysfunction.[14] Inflammatory imbalance is a major component in the pathogenesis of sepsis[15] so inhibiting inflammatory response has become a key target in its treatment.[16]

Ulinastatin is a serine protease inhibitor extracted from human urine and blood.[8,17] Ulinastatin can inhibit proteases such as trypsin, thrombin and kallikrein, which have roles in inflammation and coagulation, both critical in sepsis pathophysiology.[8] Ulinastatin can prevent neutrophil infiltration and possibly supress the MAPK (mitogen-activated protein kinases) pathway as it has been shown to inhibit the production of TNF-α, IL-1 and IL-68 making it a useful therapeutic agent. Many studies have been carried out to test the efficacy of ulinastatin administration as a treatment option for sepsis.[8,16]

Methods

Primary research papers were selected from the database Medline. Studies were included in the search if they included the key terms "septi*" (which searched for "sepsis", "septic" etc.) and "ulinastatin", "urinary trypsin inhibitor" which were published in the last 5 years. Only peer-reviewed primary research papers were selected. It was ensured that authors had published additional research in the field of sepsis to ensure competency and that, where possible, they utilised randomisation in their study to reduce bias. Since it is currently a small area of research, the search was widened to articles published

in the last 10 years and some additional papers were selected to improve the scope of the review.

Results

1. Reducing Mortality

Karnad et al suggested that ulinastatin administration could reduce mortality in patients with severe sepsis.[1] This was a randomised, double-blind, placebo-controlled trial of 114 sepsis patients. Participants either received 200,000 IU ulinastatin or a placebo intravenously every 12 hours for 5 days in addition to their ongoing treatment.[1] The 28-day mortality was significantly lower in the ulinastatin group, compared to the placebo group ($p=0.042$) and so was "new onset of organ dysfunction" (10 versus 26 patients; $p=0.003$) and "mean hospital stay" (11.8 versus 24.2 days; $p=0.001$). An earlier study using mice utilised caecal ligation and puncture (CLP) to create a sepsis model and 30 mice were split into three groups: a sham group, CLP group and CLP + ulinastatin group.[2] Their results showed that 7-day survival was significantly higher in the group treated with ulinastatin (70% versus 40%; $p=0.0187$). It was found that inflammatory cytokines, specifically TNF-α, IL-6 and IL-10, were significantly reduced following administration of ulinastatin ($p<0.05$). A recent retrospective study split 130 participants into two equal groups.[3] Both groups received the conventional treatment for sepsis, but one group received ulinastatin for 7 days in addition. Conventional treatment was dependent on symptoms but included antibiotics and ventilation. The intervention group had significantly lower APACHE II scores (mean of 6.4 compared to 11.7; $p<0.01$), which accurately predict hospital mortality.[18]

2. Reducing inflammation

Multiple studies have investigated the potential anti-inflammatory mechanism of ulinastatin in sepsis. One study investigated 263 sepsis patients with 179 receiving ulinastatin and 84 in the control group.[6] On day 3, CRPs in the ulinastatin group were not shown to be significantly lower than the control group (124 mg/l versus 83.8 mg/l; $p=0.061$). A 2017 study focusing on sepsis-induced spinal cord inflammation investigated the effect of ulinastatin on the TLR4/MyD88/NF-κB pathway, an inflammatory pathway in sepsis.[7] 120 rats were used and 110 of those underwent CLP to induce sepsis. 50 in the CLP subgroup received ulinastatin intrathecally of varying concentrations. The remaining 10 control rats underwent a sham operation, a surgical procedure where there is no therapeutic intervention. The higher doses significantly reduced TLR4 expression ($p<0.05$) and MyD88 expression ($p<0.05$) compared to untreated rats, leading to greater production of anti-inflammatory cytokines.[4]

3. Reducing organ and tissue injury

A 2019 study used 50 mice divided into five equal groups: sham, ulinastatin alone, CLP alone, and two groups received different strengths of intraperitoneal ulinastatin following CLP.5 Ulinastatin was found to significantly increase survival time (43.5 hours versus 35.2 hours; $p<0.05$) compared to untreated mice with sepsis.[5] Another main finding was that ulinastatin alleviates liver injury as in treated mice, there was significantly reduced "increase in serum levels of ALT (alanine aminotransferase), ALP (alkaline phosphatase) and LDH (lactate dehydrogenase)" ($p<0.05$) compared to CLP-only mice.[5] Histological examination reinforces this point as treated mice have a significantly lower area of liver tissue degeneration ($p<0.01$). Another study used 60 rats to model sepsis using CLP.[19] Microscopy showed that septic intestinal tissue was severely damaged, characterised by features such as "partially detached villi".

4. Ulinastatin as a combined treatment

Many studies have investigated the effectiveness of ulinastatin administration in combination with other treatments. A recent study used 60 rats, split into four equal groups.[9] All received CLP, followed by either saline, ulinastatin, glutamine or ulinastatin and glutamine combined. Sepsis symptoms were improved in all treatment groups, particularly with the combined treatment, where symptoms were mildest. Inflammation was also significantly reduced, with procalcitonin (PCT), IL-6, TNF-α and IL-1β levels decreasing the most upon administration of the combined treatment. A human study investigated a similar concept, this time with rhubarb instead of glutamine.[10] Similar methods were used, with 75 patients split into four groups; control (receiving "basic treatment"), ulinastatin, rhubarb, and ulinastatin and rhubarb combined. The level of inflammation was measured using three indicators, CRP, PCT and white blood cells (WBC) and all were significantly decreased ($p<0.05$; **Figure 1**) in treatment groups compared to the control group. However, there was no significant difference between the combined group and the other treatment groups. The same pattern was seen when comparing APACHE II score, tissue perfusion and liver/kidney function.

5. Comparing methods of administration

Some studies compare the effectiveness of different ulinastatin administration methods. The study by Yang et al in 2017.[19] involved the administration of ulinastatin either intraintestinally or intraperitoneally and the two methods were compared. It was shown that intraintestinal treatment resulted in a higher average survival rate than intraperitoneal treatment but these results were not significant.[19] A similar study divided 90 rats into five groups: sham (n=10), sepsis without ulinastatin (n=20), intraintestinal ulinastatin (n=20), intravenous ulinastatin (n=20) and two-route intraintestinal and intravenous ulinastatin (n=20).[11] The 5-day survival was noticeably higher in the two-route group, but again not significantly compared to one-route treatments ($p>0.05$).

Discussion

1. Reducing Mortality

Karnad et al provides evidence which suggests that the administration of ulinastatin in sepsis may improve patient outcomes, but does not explore the mechanism behind this,[1] unlike more recent studies such as Xu et al.[6] Karnad et al was a randomised, double-blind trial which reduces bias.[1] However, since it is a human trial, it is difficult to standardise the environment as participants received ulinastatin in addition to standard, location-dependent care. The research by Xu et al was conducted retrospectively which presents limitations as the dosage of ulinastatin and patient population being inconsistent.[6] An earlier study using mice came to similar conclusions.[2] This was a randomised study with standardised conditions which allows for reduced bias, giving us a more accurate view of the treatment effect. We can therefore infer that ulinastatin administration may contribute to reducing inflammation. This explains the improved survival rate as organ failure can be a result of the inflammatory response[20] in one model of sepsis.[15]

2. Reducing inflammation

Xu et al suggests that ulinastatin is not effective at reducing inflammation caused by CRP.[6] This demonstrates that there are limitations to ulinastatin's anti-inflammatory potential. However, Xie et al demonstrated with statistical significance that ulinastatin is effective in reducing TLR4 and MyD88 expression, suggesting that the TLR4/MyD88/NF-κB pathway may be attenuated by ulinastatin.[7] The study was random and used an adequate sample size calculated using a desired power of 0.8 which ensures the results are useful and accurate. This suggests that UTI can reduce sepsis-induced inflammation but further research into cost effectiveness is required to assess whether the impact and effectiveness of this makes it a worthwhile treatment option.

3. Reducing organ and tissue injury

Ulinastatin administration has a prominent role in reducing sepsis-

induced organ and tissue injury in murine models.[5,21] Song et al suggests with statistical significance that ulinastatin can reduce organ and tissue injury caused by sepsis.[5] The study utilised randomisation to assign mice to each group to avoid bias, which is crucial due to the smaller sample size. All mice were accustomed to a standard condition before the study which makes the of the study location less relevant and therefore the research is more applicable to a global population as location related bias is reduced. Yang et al uses microscopy to show that intestinal tissue damage was attenuated upon administration of ulinastatin.[19] Both studies demonstrate the effectiveness of ulinastatin in reducing organ injury in sepsis patients. They also share many aspects of their experimental design, including the use of murine models and using randomisation to assign treatment groups which makes the studies both reliable and comparable.[5,19]

4. Ulinastatin as a combined treatment

Wang et al demonstrates that ulinastatin has a greater therapeutic potential when used as a combined treatment with glutamine, as opposed to using ultinastatin alone.[9] However, Meng et al suggests that combining ulinastatin with rhubarb has no significantly better outcomes than using ulinastatin alone.[10] It does, however, reiterate that ulinastatin is effective at improving sepsis patient outcomes. Both studies use animal models which while useful, cannot be assumed to be comparable to a human popultation. The two studies together show that there is potential for ulinastatin effectiveness to increase when combined with another drug but more research is needed to determine which combination works best.

5. Comparing methods of administration

Liao et al shows that intestinal injury was reduced (as villus height and villus height to crypt depth ratio was the highest compared to the other treatment options) in the two-route treatment group, where ulinastatin is administered both intraintestinally and intravenously[11]. However, the 5-day survival was not significantly different when compared to intravenous administration alone. Additionally, Yang et al failed to prove any difference in outcomes when comparing intravenous and intraintestinal administration.[19] The statistical insignificance in both studies may be due to the small sample size and lack of power. If this is the case, it may provide an avenue for further research which will enable clinicians to optimise treatment based on cost, ease of use and drug efficacy whilst minimising risk of complications.

Conclusion

To conclude, most research shows statistical significance of increased survival rates of sepsis when ulinastatin is administered. The available research suggests that ulinastatin is a useful, safe, and effective therapeutic agent for sepsis and provides us with an insight into the direction of treatment options available to patients in the future. This research provides an avenue for the development of a standardised treatment to mitigate the devastating effects that sepsis can have on the human body. Although its mechanism is still not fully understood, we know ulinastatin has anti-inflammatory properties, evidenced by its reduction of inflammatory makers including CRP and TNF-α. The reduction in inflammation explains why ulinastatin significantly reduces organ injury and therefore organ failure, providing an explanation for the increased survival rate. Ulinastatin has been trailed as a combined treatment with glutamine, rhubarb, and other remedies. A variety of administration methods have also been tested. Although the results from both elements were inconclusive due to lack of statistical significance, it is possible that with further research, the optimal treatment method using ulinastatin can be determined. In further research, it will be crucial to determine many factors such as the superior administration method, timing of treatment in the disease course and safety across a variety of age groups for the best patient outcomes. This will allow for optimisation of the treatment, to ensure it remains cost effective and clinically effective.

References

1. Karnad DR, Bhadade R, Verma PK, Moulick ND, Daga MK, Chafekar ND and Iyer S. 2014. Intravenous administration of ulinastatin (human urinary trypsin inhibitor) in severe sepsis: a multicenter randomized controlled study. Intensive Care Med 40, pp. 830-838. doi: 10.1007/s00134-014-3278-8
2. Huang N, Wang F, Wang Y, Hou J, Li J and Deng X. 2013. Ulinastatin improves survival of septic mice by suppressing inflammatory response and lymphocyte apoptosis. Journal of Surgical Research 182, pp. 296-302. doi: 10.1016/j.jss.2012.10.043
3. Meng C, Qian Y, Zhang W-H, Liu Y, Song X-C, Liu H and Wang X. 2020. A retrospective study of ulinastatin for the treatment of severe sepsis. Medicine 99(49), p. 23361. doi: 10.1097/MD.0000000000023361
4. Firmal P, Shah VK and Chattopadhyay S. 2020. Insight Into TLR4-mediated immunomodulation in normal pregnancy and related disorders. Frontiers in Immunology 11, p. 807. doi: 10.3389/fimmu.2020.00807
5. Song Y, Miao S, Li Y and Fu H. 2019. Ulinastatin attenuates liver injury and inflammation in a cecal ligation and puncture induced sepsis mouse model. Journal of Cellular Biochemistry 120(1), pp. 417-424. doi: 10.1002/jcb.27396
6. Xu Q, Yan Q and Chen S. 2018. Ulinastatin is effective in reducing mortality for critically ill patients with sepsis: a causal mediation analysis. Scientific Reports 8, p. 14360. doi: 10.1038/s41598-018-32533-9
7. Xie F, Min S, Chen J, Yang J and Wang X. 2017. Ulinastatin inhibited sepsis-induced spinal inflammation to alleviate peripheral neuromuscular dysfunction in an experimental rat model of neuromyopathy. Journal of Neurochemistry 143, pp. 225-235. doi: 10.1111/jnc.14145
8. Linder A and Russell JA. 2014. An exciting candidate therapy for sepsis: ulinastatin, a urinary protease inhibitor. Intensive Care Med 40, pp. 1164-1167. doi: 10.1007/s00134-014-3366-9
9. Wang J, Zhou J and Bai S. 2020. Combination of glutamine and ulinastatin treatments greatly improves sepsis outcomes. Journal of Inflammation Research 13, pp. 109-115. doi: 10.2147/JIR.S234122
10. Meng F, Du C, Zhang Y, Wang S, Zhou Q, Wu L, Wang Y and Yang X. 2020. Protective effect of rhubarb combined with ulinastatin for patients with sepsis. Medicine 99(7), p. 18895. doi: 10.1097/MD.0000000000018895
11. Liao X-L, Danzeng Q-Z, Zhang W, Hou C-S, Xu B-B, Yang J and Kang Y. 2018. Role of using two-route ulinastatin injection to alleviate intestinal injury in septic rats. Chinese Journal of Traumatology 21, pp. 323-328. doi: 10.1016/j.cjtee.2018.05.002
12. Singer M, Deutschman CS, Seymour CW et al. 2016. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8), pp. 801-810. doi: 10.1001/jama.2016.0287
13. Rudd KE, Johnson SC, Agesa KM et al. 2020. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet 395(10219), pp. 200-211. doi: 10.1016/S0140-6736(19)32989-7
14. Jarczak D, Kluge S and Nierhaus A. 2021. Sepsis - pathophysiology and therapeutic concepts. Frontiers in Medicine 8, doi: 10.3389/fmed.2021.628302
15. Chousterman BG, Swirski FK and Weber GF. 2017. Cytokine storm and sepsis disease pathogenesis. Seminars In Immunology 39, pp. 517-528. doi: 10.1007/s00281-017-0639-8
16. Huang M, Cai S and Su J. 2019. The pathogenesis of sepsis and potential therapeutic targets. International Jounral of Molecular Sciences 20(21), p. 5376. doi: 10.3390/ijms20215376
17. Meng W-T, Qing L, Li C-Z, Zhang K, Yi H-J, Xhao X-P and Xu W-G. 2020. Ulinastatin: a potential alternative to glucocorticoid in the treatment of severe decompression sickness. Frontiers in Physiology 11, p. 273. doi: 10.3389/fphys.2020.00273
18. Tian Y, Yao Y, Zhou J, Diao X, Chen H, Cai K, Ma X and Wang S. 2022. Dynamic APACHE II score to predict the outcome of intensive care unit patients. Frontiers in Medicine 8, p. 744907. doi: 10.3389/fmed.2021.744907
19. Yang B, Gao M, Wang K, Jiang Y, Peng Y, Zhang H, Yang M and Xiao X. 2017. Intraintestinal administration of ulinastatin protects against sepsis by relieving intestinal damage. Journal of Surgical Research 211, pp. 70-78. doi: 10.1016/j.jss.2016.11.061.
20. Rossaint J and Zarbock A. 2015. Pathogenesis of multiple organ failure in sepsis. Critical Reviews in Immunology 35(4), pp. 277-291. doi: 10.1615/critrevimmunol.2015015461
21. Qiu J, Xiao X, Gao X and Zhang Y. 2021. Ulinastatin protects against sepsis-induced myocardial injury by inhibiting NLRP3 inflammasome activation. Molecular Medicine Reports 24(4), p. 730. doi: 10.3892/mmr.2021.12369

Lucy Elise Morgan

Hi! My name is Lucy and I'm a third-year medical student at Cardiff University. My current interests within medicine are paediatrics, dermatology and cardiology. I am also interested in research and am excited to explore this interest further. I also love dancing, spending time with family and friends and exploring new places!

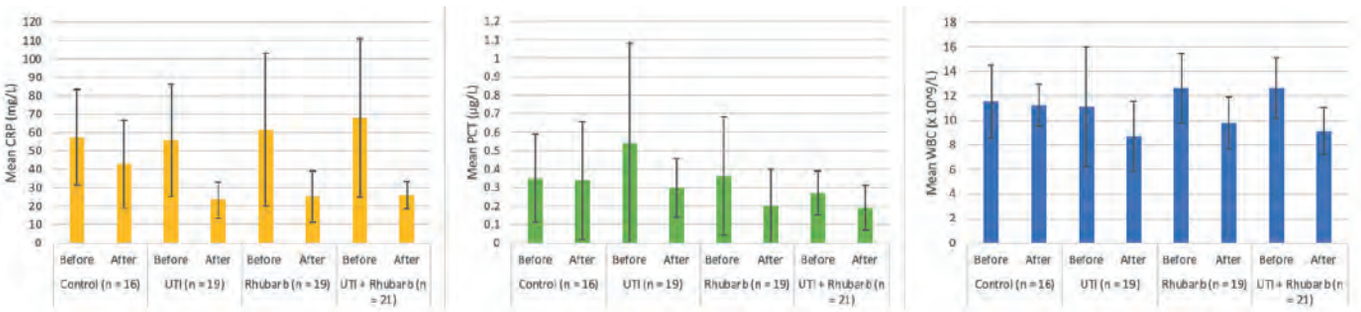

Figure 1 | Levels of inflamm tory indicators before and after different treatments. 75 patients with sepsis admitted to hospital over a 19-month period participated in this single-centre, prospective, randomised trial. They were randomly split into 4 groups; control, ulinastatin (UTI), rhubarb and ulinastatin and rhubarb combined. Each group received the basic treatment, consisting of treatment for the primary disease (including antibacterial drugs), respiratory support, electrolyte and acid-base balance correction and treatment for any existing diseases. The UTI group received basic treatment alongside 200,000 units of ulinastatin three times daily. The rhubarb group received 12g of rhubarb once daily alongside basic treatment. The UTI + rhubarb group received basic treatment, ulinastatin administration and rhubarb. The level of inflammation was measured over 5 days using 3 indicators, C-reactive protein (CRP), procalcitonin (PCT) and white blood cells (WBC). The figure illustrates the starting (before treatment) and ending (after 5 days of treatment) values of these indicators with error bars representing standard deviation.
Figure created using data from Meng et al 2020.[10]

Feature

Dentistry in Delhi

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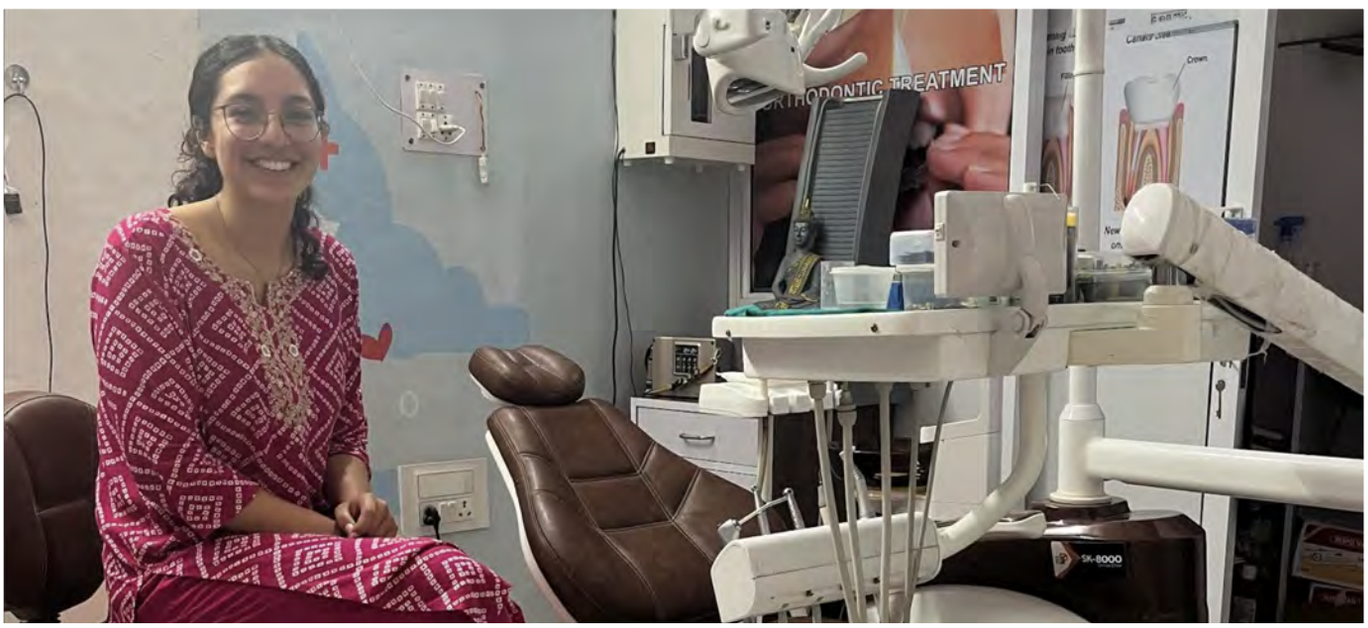

Out with the old and in with the new

This summer, I took it upon myself to venture to Delhi, India, and organise a dental placement. This placement was about more than just honing my clinical skills, it was about immersing myself in a new cultural and professional environment, challenging myself to adapt, and gaining insights into the global disparities in healthcare. As a second-generation immigrant, I have been visiting India since I was a young girl. My mum used to tell me how, when she grew up, they used sticks from a neem tree to clean their teeth. You chew on it until it starts to fray like the bristles of a toothbrush. The other option was charcoal on salt which you would scrub over your teeth with a finger, surprisingly, this option apparently tasted nicer! Whilst these practices may still be used in certain parts of India, dentistry otherwise has changed massively since then. At my family home in India, we're now using fluoridated toothpaste and manual toothbrushes. At the local school, children are taught to brush their teeth twice daily using a toothbrush and fluoridated toothpaste. Moreover, the practice I worked at was well advanced in its dental equipment, a pleasant surprise for me, and a reflection of how much dentistry has progressed in India.

Accessibility and infrastructure

However, from the state of dentitions I witnessed over my two weeks of dentistry in Delhi, there still seems to be a lack of oral health awareness, prevention is not the priority for these patients and there is still plentiful progress to be made. Whilst the dentist I worked with was well informed of the importance of prevention and regular checkups, he explained that despite advice, his patients only ever came to the dentist when they are in pain or for other emergency treatment. For context, I was working at a small private practice with just one dental chair in a moderately affluent area. In an area like Delhi, a lack of dentists and appointment availability did not appear to be the issue. In fact, there is almost an oversubscription of dentists and doctors, quite the contrary to our access issues in the UK. In this densely populated city, I noticed that within walking distance there might be multiple dental or medical clinics. From speaking to local dentists and doctors, it seems due to their vast availability and the increased population density, many healthcare professionals specialise in a certain field of dentistry or medicine, so they can offer specialised services as there is high demand and competition between local practices. I noticed that, compared to the UK, particularly for the medical field, this made accessing healthcare much more efficient and streamlined.

There are also government hospitals in which medical and dental care is provided, often at lower rates to private practices, however, private practices cover the majority of dental care in Delhi. However, I was unable to witness how their government hospitals operate, so I am unable to make a comparison in that respect.

So, if a lack of dentists in this area of Delhi is not a significant barrier to accessing a dentist, what are the possible reasons for patients not attending for regular checkups?

There are many possible reasons for this, here are some examples taken from 'Barriers to access dental care services among adult population: a systematic review, a study conducted across the Indian population'[1]:

- Financial issues
- Afraid of the dentist
- Attitudes and beliefs towards dental care
- 'No issues' with teeth
- Lack of time
- Work restraints
- Not a priority

Each individual factor combined with a lack of oral health awareness will inevitably lead to a lack of preventative care and result in emergency-based treatment.

Differences in practice

Whilst practices in the UK and India are largely similar, there are some hygiene regimes that would be considered sub-optimal compared to those in the UK, for example the dental chair and bracket table were not disinfected between patients. Furthermore, the bracket table permanently housed a sheet and an array of materials such as endodontic files (boxed) and the local anaesthetic (LA) vial, but these were not moved or wiped between patients, despite being in close vicinity during aerosol-generating procedures. There were other questionable practices, for example, not using LA for a subgingival crown prep (non-vital), even if the patient looked or felt uncomfortable, they did not ask for local anaesthetic, the patient just deals with being uncomfortable, which seemed normalised. Furthermore, never using rubber dam for any endodontic procedures, moreover, not even attaching floss to the file if you are not going to use a rubber dam. On questioning, the dentist explained that sodium hypochlorite diluted with saline is used for disinfection and cotton wool is used to isolate to tooth and prevent hypochlorite injury. They showed me radiographic evidence of many completed root canals and the post-ops and, whilst they were not claiming all their root canal treatments are perfect, they reassured me that they are doing what they are intended to do: save the tooth and get the patient out of pain. I would just like to reiterate that these observations may not be representative of the rest of Delhi or India. Whether this is the standard students are taught in India or if it was the individual practice, I am not sure. Whichever it is, it seems to work for them but arguably falls below the standard of which we are taught in the UK. There are certain things I questioned the clinician on, where I felt comfortable, but not knowing the teaching and standards of care in India, I did not want to cross the line and make the dentist feel like I was undermining their practice.

Challenges and learning

Whilst being a well-established practice and a more developed area of Delhi, it still faced challenges that I take for granted living in the UK. For example, we endured electricity cuts, extreme weather conditions and flooding meaning the dental practice had to close. A memorable time being when I had put cement in a crown, and we had a power cut. I had no choice but to cement the crown whilst using the patient's phone torch as a light! In situations like this, it is unpredictable as to how long you'll be waiting for the power to come back. This meant sitting in stale humid, heat with no fans, no AC, just waiting for the lights to come back. However, this seemed like a common thing to patients here and they were not fazed by it like I was! No doubt I learned to navigate the complexities of a healthcare system different from my own, adapt to new environments and overcome challenges.

Summary

I found this experience incredibly enriching; not only did I learn many clinical tips and tricks from another clinician; I gained an insight as to how dentistry operates in Delhi. I witnessed its efficiency and ability to adapt to the ever-changing technology and practices within the dental world. Conversely, I also saw areas for development, particularly in educating patients on the importance of oral hygiene and the link between paan and oral cancer, but I appreciate these issues are deep rooted and will take building of habits and education from an early age to see significant change. Hopefully, as dentistry in India is progressing, we will see a change in attitude towards oral hygiene in the years to come. I was generally impressed with the dental practice I observed, despite some differences in procedures which was expected. It was very well equipped and of a decent standard, however, it was still mediocre compared to most dental practices here in the UK. This made me appreciate our facilities in the UK more than ever, particularly at Bristol Dental School. I feel ever so fortunate to study at such a well-established institute with modern equipment and technology and just a magnificent building overall. Finally, I am extremely grateful to have had this opportunity and experience, it has reinforced my passion for delivering accessible, quality dental care – no matter where in the world I am.

References

1. Krishnan L, Aarthy CS, Kumar PD. Barriers to access dental care services among adult population: A systematic review. J Global Oral Health 2020;3(1):54-62 doi:10.25259/jgoh_1_2020.

Deepa Sharda

Hello! My name is Deepa and I am a fifth-year dental student at the University of Bristol. Unlike most dental students, I studied A-Level English Literature and have always had a love for writing and the world of academia. Teaching and education are definitely my passion. For 2 years I voluntarily worked with students with English as a second language; I now work with the University of Bristol as a Widening Participation tutor, encouraging students from less advantaged backgrounds to study health sciences/dentistry. I resonate with these students and understand some of the barriers they face, hence feel joy in giving back. I love to share my enthusiasm and passion for dentistry with the younger generation and hope to do this through the INSPIRE journal too. I'm so grateful to be a part of the INSPIRE scheme, helping to spread fantastic research, educate others and learn a lot myself!

Report

Inspiring students in research

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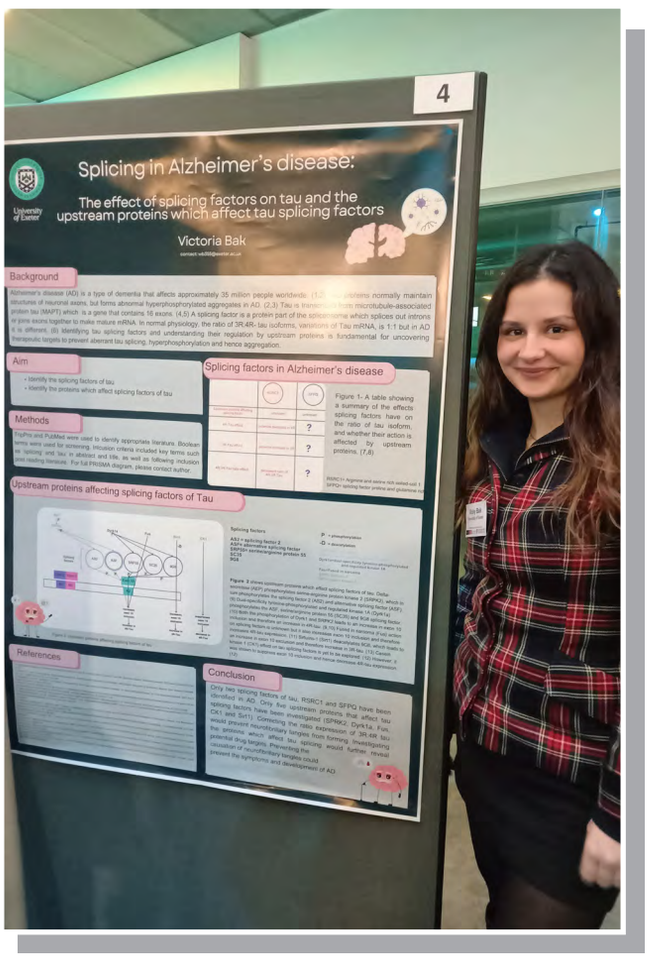


The Inspire conference took place on Saturday 23 November 2024 at the University of Plymouth.

In total, 185 medicine, dentistry and veterinary students from the University of Bristol, University of Exeter, University of Plymouth and Cardiff University came together to showcase their research projects and interests.

The morning began as expected, with students setting up poster presentations and enjoying coffee and treats—a much-loved feature for us students!

Following a warm welcome and introduction by the INSPIRE leads, Dr Becky Foster (Bristol), Dr William Davies (Cardiff), Dr Jane Smith (Exeter), Professor David Parkinson and Professor Vehid Salih (Plymouth), the short oral presentations commenced.

Throughout the day, several oral presentations were delivered, each covering diverse specialist areas and topics. The winning presentation, given by Nada Dahan (Cardiff University), focused on the management of patients with type 1 diabetes, titled 'Does retained endogenous insulin secretion, measured using c-peptide lead to improved quality of life and reduced healthcare utilisation in recently diagnosed type one diabetes?'.

Nada Dahan's comment:

> "During my INSPIRE open day, I visited the Exeter Centre of Excellence for Diabetes Research (EXCEED) and was inspired by the passion and innovation of the team. Observing leading specialists in the field fuelled my interest in diabetes research and motivated me to undertake a summer project with Dr. Angus Jones and Julieanne Knupp. My overall finding was that early retained c-peptide is associated with markedly reduced hospital admissions and improvement in glycaemic control in adult-onset type 1 diabetes but does not impact quality of life measures.
>
> "The project was a steep learning curve, from learning to code from scratch to presenting my findings to professionals, but it taught me invaluable skills in research, data analysis, and presentation. I am incredibly grateful to everyone involved in the INSPIRE scheme for this opportunity, which has strengthened my ambition to pursue a career as an aspiring clinical academic."

In addition to the oral presentations, there were also four Hackathon teams presenting their innovative solutions for improving the mental health and wellbeing of doctors working in healthcare.

Tragically, we learnt that approximately one doctor dies by suicide every three weeks. Clearly, this issue needs a truly effective solution. At one point, a member of the audience remarked, "Shouldn't doctors just be more resilient?" Whilst their tone was only used to provoke a discussion about potential dismissal of doctors mental health, this was a grounding statement, especially from the point of view of a medical student about to enter this profession in a few years' time.

The University of Exeter team proposed the use of AI to ease the administrative workload of NHS doctors. Below, Shloka Doshi, a year 3 medicine student from University of Exeter, describes her participation and journey through the Hackathon:

"Recently, I had the privilege of being a part of the University of Exeter Hackathon team, participating in the INSPIRE Research Conference 2024. This collaborative event brought together students and faculty from the University of Plymouth, Cardiff University, the University of Bristol, and the University of Exeter.

"Why I chose to participate in INSPIRE: coming into year 3 meant this September I began my clinical hospital placements— a milestone I approached with excitement and apprehension. Reflecting on my first term, I've come to appreciate the importance of time management and organisation to avoid burnout. Hence, coming across this year's hackathon topic, 'Offer practical interventions to tackling mental health and loss from medical, dental, and veterinary professions,' resonated deeply.

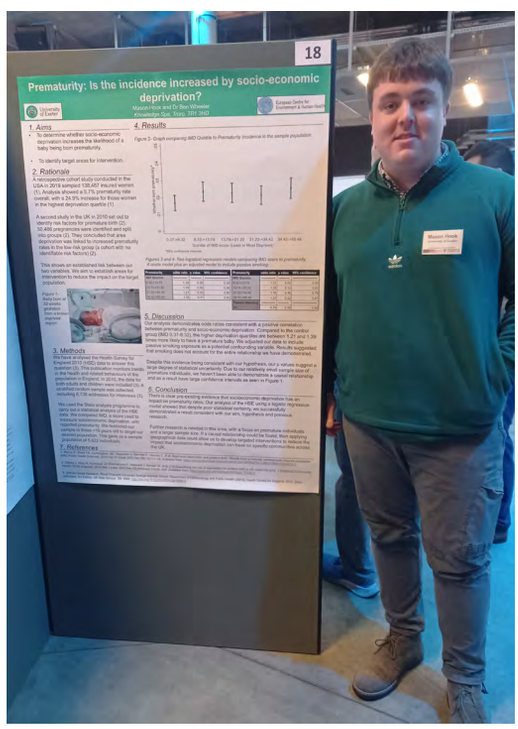
"Choosing our idea: our hackathon journey began two weeks before the conference with an initial meeting in Exeter. The team comprised of students across different stages of medical school: Taiwo and Aaisha (Year 1), Ismail (Year 2), and Rose, Ethan, Jack, and myself (Year 3). This diversity was a distinct advantage, as it allowed us to approach the topic with varied perspectives and experiences.

"After brainstorming potential solutions, we identified a pressing issue which was the administrative burden contributing to burnout among clinical professionals. We decided to choose our topic, as currently 70% of a resident's time is being spent completing administrative tasks. Artificial Intelligence (AI) is a technical and scientific field that has recently seen major advancements in medicine. Therefore, our solution offers leveraging Artificial Intelligence (AI) to aid in these tasks, thereby freeing up clinicians to focus on patient care. Each team member took responsibility for a specific area of research. My role involved explaining the value of artificial intelligence within healthcare systems, specifically focusing on how voice dictation and AI software to summarise patient records could significantly be used to reduce admin load. Over the next two weeks, we collaborated through virtual meetings to refine our ideas and create a cohesive presentation. I had the chance to work in a team with colleagues who were incredibly motivated in achieving a shared goal.

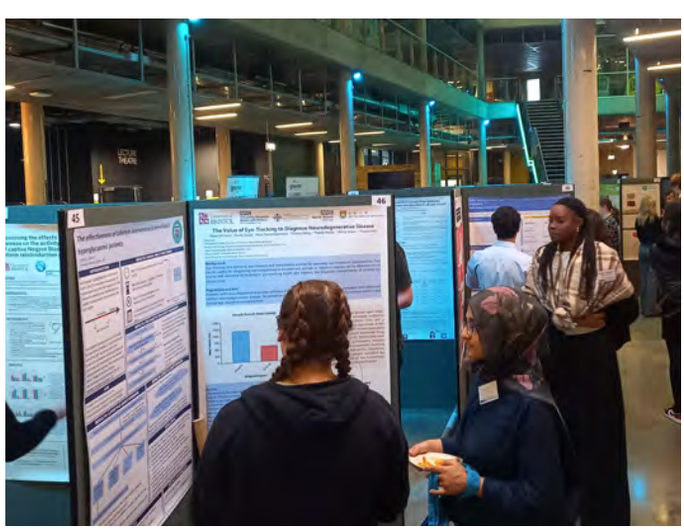
"The INSPIRE Conference Experience: the INSPIRE Conference took place on 23 November in Plymouth. As a presenter for the Hackathon team, I started the day filled with nerves but also excitement. The conference featured outstanding presentations by students from all four universities, showcasing a wide range of innovative ideas. This was followed by Hackathon presentations. Being able to successfully present our idea to future Doctors, Vets and Dentists, and Esteemed Faculty Members was a truly rewarding experience. Our idea was challenged with thoughtful questions and lots of support. The dedication and effort of everyone resulted in a presentation we were very proud to deliver.

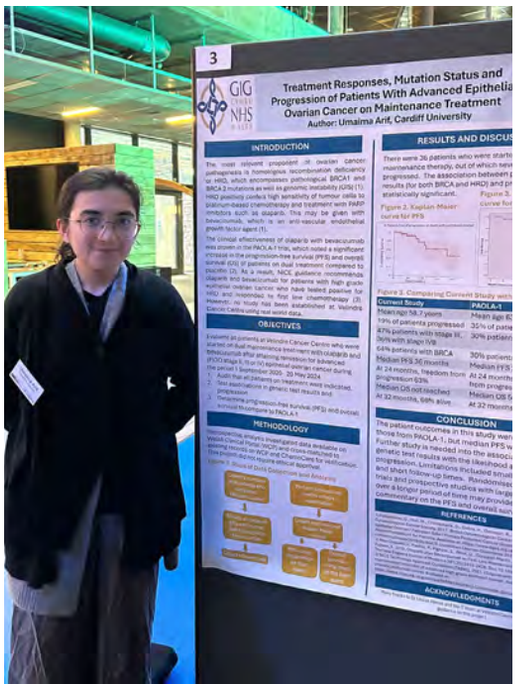
"Later, we had the opportunity to engage with poster presentations and network with other students. The depth and quality of research presented was truly inspiring. From neonatal neurodevelopment and deep brain stimulation, to tackling diversity in dermatology, the novel research of students from all universities was an eye-opening experience into medical, dental and veterinary research and its vast opportunities.

"Will I attend the INSPIRE Conference again? Most definitely. The INSPIRE conference is an opportunity to not only participate in but also learn about academic research conducted by students. It provides an insight into innovative ideas and new advancements within healthcare, dental and veterinary fields."



Throughout the day, there were several poster presentations displayed for students to explore during the coffee breaks. Umaima Arif shared a reflection on her experience.





"I had the honour of attending the INSPIRE conference at Plymouth and presenting my poster on the research I conducted before the summer of my fourth year as a medical student. This research was an audit and evaluation of all patients at Velindre Cancer Centre who had been started on olaparib and bevacizumab for the maintenance therapy of advanced epithelial ovarian cancer between 1 September 2020 and 20 May 2024, including examining their progression-free survival and overall survival while comparing them to the original trial that confirmed the clinical effectiveness of this dual therapy on patients who had attained remission. I found the experience of attending the conference, sharing my research, and learning about other people's research both enlightening and enjoyable. During the period of oral poster presentations, students circulated around different posters and listened to 5–10-minute speeches about the aims, findings and future considerations of their projects. It was a wonderful opportunity for me to explore other areas of similar and different studies, including those of students who had studied oncology for their student-selected component projects as well. It was clear that all students had worked very hard to not only conduct interesting investigations into topics of their choice and ponder the implications of their work deeply, but to summarise and present it in a concise and coherent manner that engaged other students and professors. As systemic anti-cancer therapies and maintenance treatments are a rapidly growing field of research, I was excited to learn about students who had similar interests to me and further opportunities for networking were provided through a panel session that included an Oxford-educated clinical academic as well. Overall, I was grateful for this opportunity to present my research to an audience and learn from both the poster and oral presentations of others."

Finally, prior to the awards being handed out, a panel discussion took place where students had the opportunity to ask questions about academic careers for physicians. Speakers included Prof Helen McShane (Oxford), Dr Claire McIver (Cardiff) and Dr Victoria Haunton (Plymouth).

The day was an overall success, truly encouraging students to further actively engage in research.

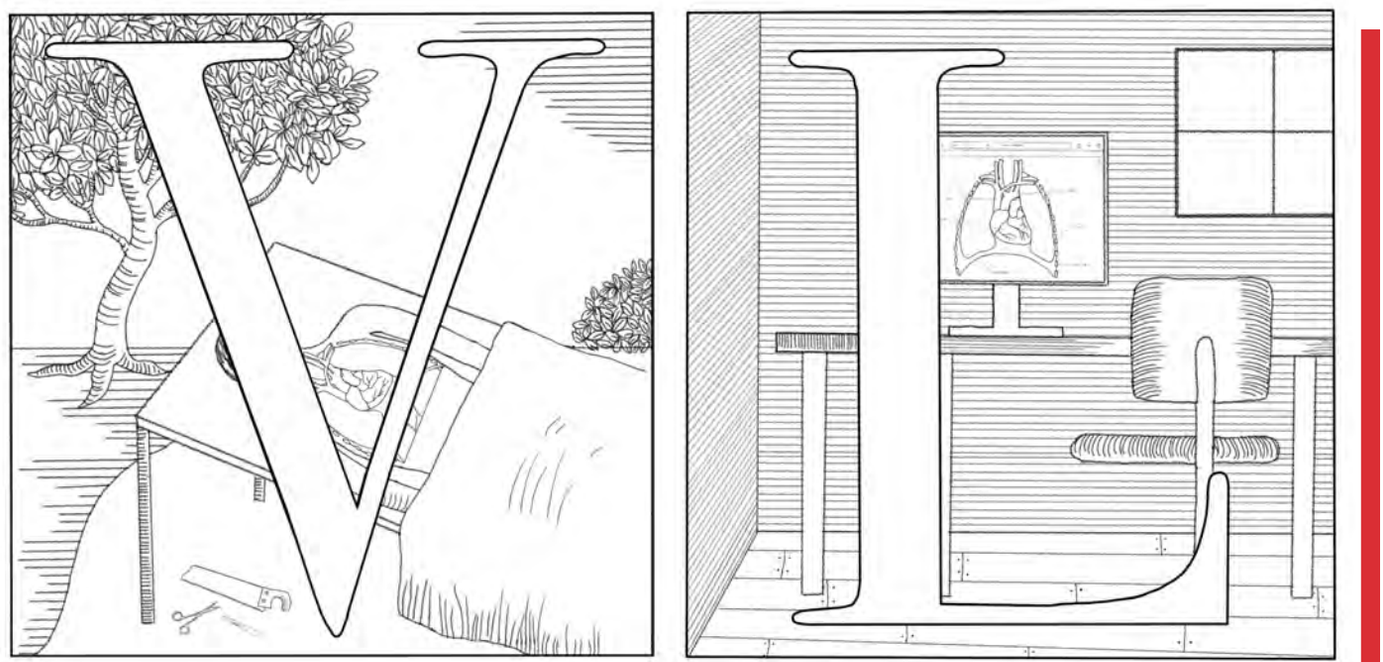
Prizes for the best oral and poster presentations:
1st Place Oral: Nada Dahan, Cardiff University.
2nd Place Oral: Agung Bate, University of Exeter.
1st Place Poster: Fejiro Okagbare, Keele University.
2nd Place Poster: Mason Hook, University of Exeter.
The Cardiff University Team won the Hackathon challenge.

With thanks to Victoria Bak, Shloka Doshi and Professor David Parkinson for the photos, and to Professor Parkinson for assistance with this report.

Sponsorship for the conference came from Sanofi, Greiner and the MDU/DDU.

Creative

Art by Laura Munn, University of Exeter



I created this artwork as part of my medical humanities module 'What can history tell us?' at the University of Exeter. This module encouraged me to consider how our medical knowledge has evolved over time and reflect upon the importance of evidence-based medicine for continual medical advancement. I was inspired by the work of Veslius in his book 'De humani corporis fabrica libri septem' and how he has influenced modern medicine.[1] Therefore, I decided to create a piece of art that compares my experience of current anatomical education with Vesalius' work during the Renaissance.

I was fascinated by his use of decorated initials, which he used to illustrated his methods to the reader, including the more controversial aspects such as robbing graves.[2] I used this concept within my artwork to help me compare 'then' and 'now' and to highlight the lasting impact of Vesalius.

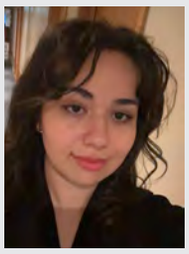
My medical humanities module has encouraged me to question my attitudes towards learning, and I hope that my art will encourage you to do the same. As physicians, if we are not continuously questioning our current practice, then we are doing a disservice to our patients and the profession. In future, instead of thinking "it's a fact," I will consider how we ascertained the information and where there are opportunities for further discovery.

References

1. Vesalius A. De humani corporis fabrica libri septem. Basle: Per loannem Oporinum; 1555. 824 p.
2. Wellcome Collection Eleven decorated initials from the Basel 1555 edition of Andreas Vesalius's De humani corporis fabrica. Woodcuts, 1555. [No date]. [cited 2025 Jan 25]; [1 screen]. Avaliable from: https://wellcomecollection.org/works/xjwvmjqs.

Senior Editors, Winter 2024/2025

Hajer Al-Shakarchi



Year 4, Dentistry, Cardiff University

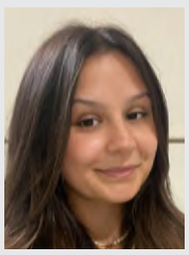
Hello, I am Hajer going into fourth year of dentistry at Cardiff University! Within dentistry, my interests comprise maxillofacial surgery and cosmetic dentistry. As an inquisitive student with a passion for lifelong learning, I saw INSPIRE as a great opportunity to gain some insight into research and editing. I am eager to learn from other people and to contribute my expertise in editing when reading other students' papers. Outside of dental school, I enjoy going on walks and I also run a social media page to document my journey as a dental student and the progress I make.

Umaima Arif

Year 5, Medicine, Cardiff University

Hi! I am a final year medical student with a heavy passion for research, writing and travel. My current clinical interests include internal medicine and oncology as well as global health and humanitarian medicine. Most recently, I have been interested in the role of immunotherapy and biologic therapy for gynecological cancers, which has been the focus of my recent SSCs and my current elective in Canada. Because research publication and writing has always been a particular passion of mine, I deeply appreciate being part of the editor team for the INSPIRE Student Journal, as it enables me to encourage other students' research interests as well as spread the word regarding new prospects and versatile developments in different fields - something I believe to be the core of one's medical career. Outside of the journal, I try to further my experience through peer-reviewing, leading research in the Refugee Health Society, and teaching for Cardiff Muslim Medics. I hope that further experience will enable me to grow into a well-rounded, conscientious practitioner who is open to learning more about the world and my colleagues' impressive works.

Victoria Bak



Year 2, Medicine, University of Exeter

I am currently a second-year medical student and my interest in research began in my previous degree where I studied Medical Sciences at the University of Exeter. I enjoy learning about a various number of topics including neuroscience, women's health, dermatology and preventative medicine. Being an editor for the INSPIRE journal has reinforced my desire to pursue a medical career in both a clinical and academic setting. Learning how the journal is assembled from behind the scenes as well as reading the written pieces has been interesting. Outside of my studies, I enjoy going to the gym, reading, playing the piano and travelling.

This edition of the journal, shows a broad range of scientific highlights. I hope you find these contributions both insightful, like we have, and appreciate that such research will ultimately underlie how clinical practice will exist in the near and far future. Enjoy the read!

Dilshan Jayakody

Year 5, Medicine, University of Plymouth (On to Intercalation - Master's in Cardiovascular Research, King's College London)

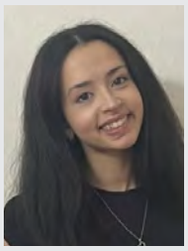
My journey in medicine is driven by my passion for addressing health disparities and inequalities, and I'm deeply involved in several research projects aimed at improving healthcare outcomes for our vulnerable populations. I am also passionate about quality improvement projects in planetary health and sustainability. My research interests led me to discover INSPIRE, and I feel honoured to be part of a likeminded editorial team.

In the future I aspire to become a surgeon, with interests in trauma surgery and cardiothoracic surgery. In my free time, I love cycling and mountain biking, enjoying the thrill of navigating challenging terrains. I also really enjoy watching sports, whether it is live or down at the pub with friends!

My experience working with INSPIRE has been incredibly enriching. I've gained valuable skills in copy-editing, social media management, and interview/podcast. I've thoroughly enjoyed every aspect of handling submissions from our talented peers across the GW4 and around the world.

I hope readers find as much joy in reading this issue of INSPIRE as we did in creating it!

Tayha Jupe



Year 4, Medicine, University of Bristol

Hello, I am Tayha, a fourth-year medical student at the University of Bristol. During my intercalation, my interest in research grew, leading me to join INSPIRE as an editor. I've thoroughly enjoyed gaining insights into the publication process and understanding the journey a paper undergoes from submission to acceptance. My interests include dermatology, plastic surgery, women's health, microbiology, and pharmacology, making this role a perfect opportunity to explore these fields further. Outside of my studies, I enjoy reading and playing badminton. INSPIRE is an excellent platform for students to engage with research, and I encourage everyone to explore its content. Research is vital to advancing all areas of medicine, especially as we move towards a more sustainable and evidence-based healthcare system.

Sophie Lawrence

Year 3, Medicine, University of Plymouth

Hello, I am Sophie, a third-year medical student at Peninsula. I initially got involved with INSPIRE through the research program, which eventually led me to do a summer project with the same lab. My current research interests include cancer endocrinology and the role of APP in the pathogenesis of Alzheimer's, breast and prostate cancer. I have enjoyed my time as the editor for the INSPIRE journal and have found it fascinating to read the research papers from various universities and explore new and innovative research. Outside of medical school, I love running and anything else outdoors, including walking my three cockapoos.

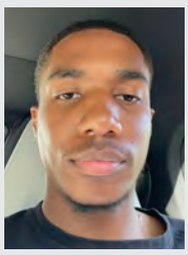
Alvin Leung

Year 4, Medicine, University of Bristol

Hi! I am a fourth-year medic from the University of Bristol. My main clinical and research interests are dermatology and venereology, and I am also passionate about tackling inequalities in healthcare. It has been a pleasure working as an editor for the INSPIRE Student Journal, perusing through the innovative literature that we have received, as well as delving into topics that are less familiar to me previously. In my spare time I enjoy travelling, strolling in art galleries and a nice cup of coffee.

Senior Editors, Winter 2024/2025

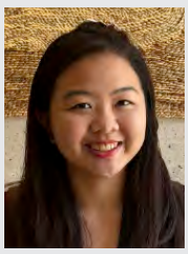
Mafa Mohlala



Year 2, Dentistry, University of Plymouth

I am a second-year dental student at the University of Plymouth. I became engaged with academic research during my previous degree, Medical Pharmacology, in which I was able to contribute to research as part of my dissertation. This curiosity and intrigue did not leave me and when the opportunity arose, I decided to take on the role of editor as part of the INSPIRE student journal. I have thoroughly enjoyed the process of learning about the behind-the-scenes processes of academic writing from submission to acceptance. My current academic interests include oral medicine and maxillofacial surgery. In my spare time I enjoy Muay Thai (Thai kickboxing) and playing football.

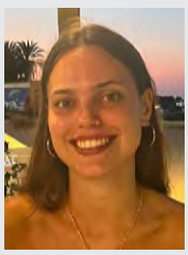
Eunice Pak



Year 5, Medicine, Cardiff University

Hello! I am Eunice, a final year medical student at Cardiff University aspiring to be a clinical academic. Within medicine, I like the fields of internal medicine and children's health. I have previously undertaken research work in clinical pharmacology and paediatrics, having presented in several international conferences. Being an editor for the INSPIRE journal has enabled me to understand the process behind publications, working with an excellent team of editors and reviewers to produce the manuscript in your hands. I also enjoy teaching, opening my eyes to new medical innovations and reading about, or even producing, works on medical humanities- including art, music, literature and history. In my spare time I enjoy hiking, watching tennis, listening to music, singing, playing board games and maintaining my blogs.

Sasha Scott



Year 3, Medicine, University of Exeter

Hi, I am a third-year medical student at the University of Exeter. I am currently interested in psychiatry and anaesthetics, but hope that my upcoming placement years will provide me with a bit more clarity about which area I would like to specialise in! Outside of medicine, I love to read, dance, draw and get outdoors. I've really enjoyed being an editor for the INSPIRE student journal, as it has been fascinating to see the behind-the-scenes of the publishing process in research. I have loved reading all the work that has been sent in, and hope you enjoy our new issue as much as we have creating it!

Eva Ruiz-Daum

Year 5, BMBS, University of Exeter

My name is Eva and I am a fifth-year medical student at the University of Exeter. I have loved spending my time as a student journalist meeting with scientists and consultants with incredible insights into the world of health, both from their research and career paths. I was lucky to also begin to develop skills in copy-editing and appraising incoming submissions. Although I am open minded to all specialities I am especially passionate about internal medicine. My hobbies outside of medicine include drawing, classical guitar, learning languages and swimming, and I am hoping to take up surfing during my placement in Cornwall this year.

Deepa Sharda

Year 5, Dentistry, University of Bristol

Hello! My name is Deepa and I am a 5th year dental student at the University of Bristol. Unlike most dental students, I studied A-Level English Literature and have always had a love for writing and the world of academia. Teaching and education is definitely my passion, for 2 years I voluntarily worked with students with English as a second language; I now work with the University of Bristol as a Widening Participation tutor, encouraging students from less advantaged backgrounds to study health sciences/ dentistry. I resonate with these students and hence feel joy in giving back. I love to share my enthusiasm and passion for dentistry with the younger generation and hope to do this through the INSPIRE journal too. I am so grateful to be a part of the INSPIRE scheme, helping to spread fantastic research, educate others and learn many things myself!

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