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FOREWORD

Modern medicine is a far cry from humanity's first dalliances with healing practices. From paleontological records of psilocybin use, to the first recorded surgery in the Stone Age, to the invention of vaccines, medicine is in a continual state of metamorphosis, reinventing itself at every turn. As students of today's medicine, we have the luxury of looking back on its vast, rambling history from a place of unprecedented scientific insight and global connectedness.

Gone are the days of believing a lobotomy will treat a young child's seizures just as well as a grown man's schizophrenia or that bloodletting will cure both a teacher's pneumonia and a farmer's arthritis. It's difficult to say exactly what forces have driven medical discovery forward in lock step with the rest of human achievements in technology, agriculture, art, science, and engineering. Is it humanity's innate curiosity that demands this progress, or has medical progress allowed humanity the safety and longevity to seek innovation in other fields? While we may never know the answer, we can be certain that medicine is unlike any other domain of human inquiry. Gravity remains constant, the earth orbits the sun every 365 days, crops will always need rain, but medicine seeks a solution to 8 billion unique and ever-changing problems. With that daunting mandate, we find ourselves on the precipice of medicine's next great frontier; treating not just the disease, but its unique manifestation in each individual.

Thankfully, we are not alone, and today's global village of scientists, clinicians, engineers and entrepreneurs are working tirelessly to develop solutions to medical problems tailored to the individual. We are now hearing stories of a patient's cancer being cured by their own cells, genetically reprogrammed to attack their tumour, or using a patient's unique genetic makeup to predict how they will respond to a medication. By curating the Student Medical Journal's first special feature, we hope to inspire the students and faculty of UCC, and the wider academic community to play their part in this ever-evolving field, pulling back the curtain on the potential of personalised medicine and a new era of patient care.

We would like to sincerely thank the UCC School of Medicine for their support and encouragement in the generation of this journal. Additionally, a very warm thank you to all our faculty and peer reviewers who took the time and effort to critically appraise the submissions for this edition, without which this publication would not have been possible. This journal would also not have been possible without the students and faculty members who submitted their scientific research to this edition. Finally, we would like to thank our readers, for whom we do this, and who keep the journal alive from year to year. Thank you and happy reading.

Kind regards,

Shobha Mehta & Pádraig Cronin

SHOBHA MEHTA & PÁDRAIG CRONIN

Co-Editors-in-Chief

Address

I would like to thank the UCC Medical Research and Technology Society for inviting me to write the opening address for the 2024 edition of the UCC Student Medical Journal. It is an honour to contribute to this excellent publication, and especially on this year's theme of personalised medicine.

Personalised medicine, or precision medicine, has been heralded as the future of healthcare. It aims to move away from the 'one size fits all' approach to the treatment of a particular condition, and rather follow an approach which tailors medicine to individuals or subgroups of patients. Personalised medicine can only become a practical reality due to scientifically robust and ethically-sound research. Translational medicine- the route by which discoveries are translated from molecular and cellular experiments, through preclinical studies, clinical trials and ultimately into healthcare practice- is at the core of all advances in healthcare and is crucial to the success of personalised medicine. It is important that the information flow is bidirectional. Moving the findings of clinical trials, especially unsuccessful ones, and from epidemiological or population health studies, is critical to the ongoing development, finetuning and implementation of personalised medicine. As a researcher and educator in the field of translational medicine, I am optimistic about the future of personalised medicine and its potential to improve outcomes for individual patients and for our society.

I am fortunate that my academic position in UCC allows me to meet, educate and work with bright, talented students of science, medicine, pharmacy and many allied health disciplines. I would encourage all undergraduate students to take every opportunity possible to experience research. Academics are almost always happy to facilitate students who show a keen interest in research. Being involved as part of a research team, for example, during a summer studentship or internship, or simply to shadow a postgraduate or postdoctoral researcher in a lab, allows students a taste of what research is like. It enables them to develop transferable skills such as how to source and distinguish data generated from robust and ethical research, to critically appraise this, and to apply it to healthcare practice.

Interdisciplinary research is crucial for the advancement of personalised medicine. The complex problems that arise in translational medical research are more easily solved by addressing them from multiple, diverse perspectives. Indeed, there is an increasing emphasis on incorporating interdisciplinary education into our curriculum. This fosters skills such as team-working, problem-solving and innovation, equipping our students for their future workplaces, where open communication and sharing of different skill sets, methodologies and knowledge bases will be expected. Incorporating the experiences and viewpoints of doctors, nurses, pharmacists and scientists to the development of personalised healthcare is crucial to ensure that research findings are translated into the best possible clinical practices, resulting in optimal outcomes for the ultimate stakeholders, that is, the patient and society as a whole.

In order to develop and implement personalised medicine into healthcare, complex and multifaceted issues will need to be addressed. Areas such as informed consent, data stewardship and privacy, as well as the potential role of artificial intelligence in research and in healthcare, need to be considered.

In parallel, important work needs to be done to ensure that personalised medicine is accessible to all patients, regardless of their gender, race and socioeconomic status. Careful consideration of the intersectionality of gender and race with social, genetic and environmental aspects which affect an individual's susceptibility to certain diseases, as well as their access to healthcare, will be a major challenge. This can be helped by incorporating diversity, equality, and inclusion into all stages of research, from study design and participant selection, through data collection and interpretation, to implementation within our healthcare systems and infrastructures.

Finally, I cannot overstate the importance of communicating scientific research to the public and to patients, in a transparent manner that is easily understandable. I am very keen that our students graduate with skills and competencies in these areas. It is crucial to involve patients in the design and conduct of research - from laboratory studies to clinical trials - and in disseminating research findings to the public. My research programme is focused on developing disease-modifying therapies for Parkinson's, a common debilitating and uncurable neurological disorder. I have the pleasure of working with many people with Parkinson's, engaging with them to inform the design of our studies and to aid the dissemination of our findings. Communicating with patients and the public is invaluable to research, for sharing information and ideas, and in particular for considering the lived experiences of patients, which has greatly improved and enriched my research and its outcomes. Greater participation by patients and their carers in research will be important to advance personalised medicine that is equitable and accessible to everyone.

Professor Aideen Sullivan

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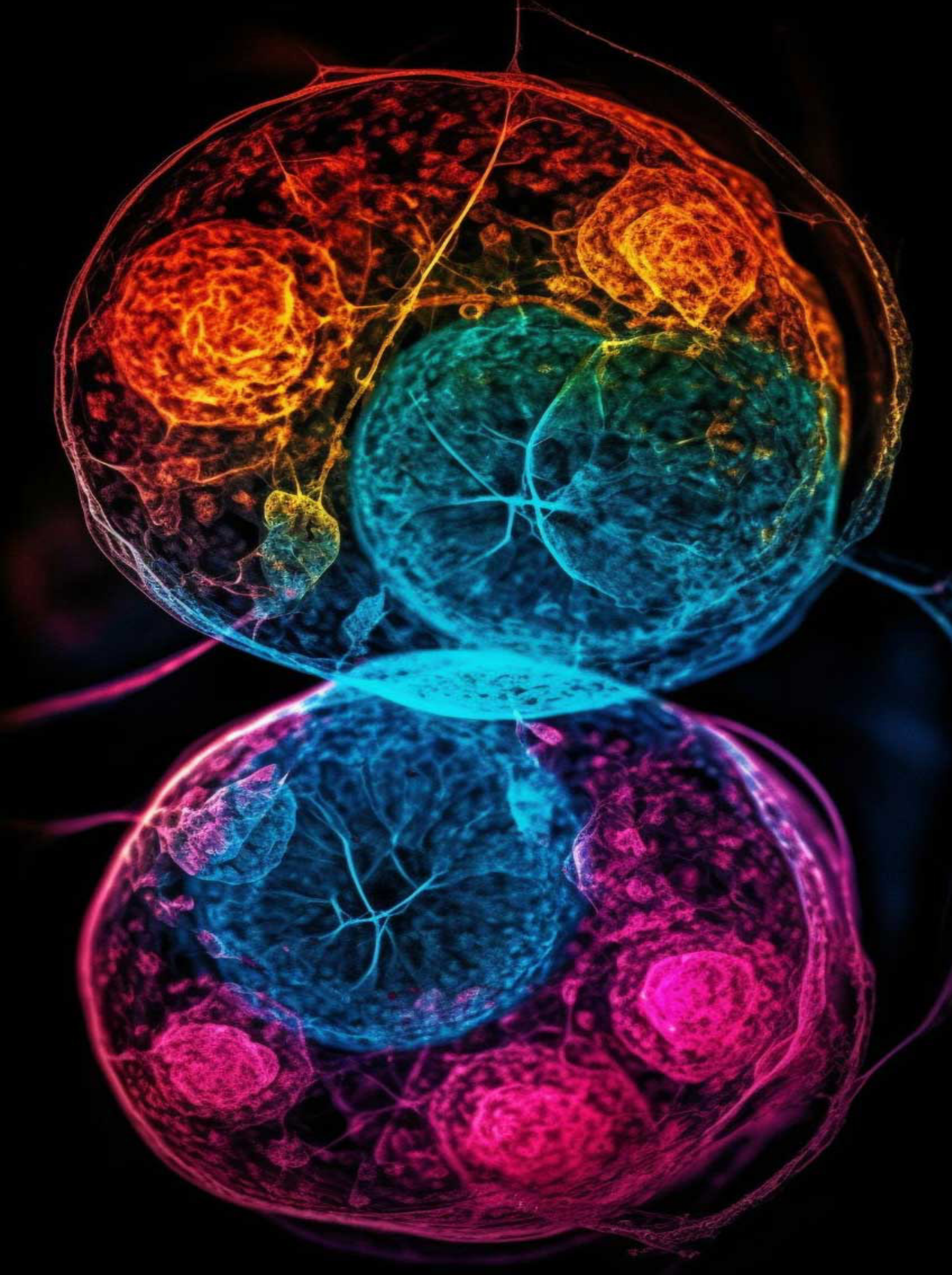

An Exploration of Gut Hormone Therapy to Treat Infertility Caused by Type 2 Diabetes

ALISON BELLE MARTIN, DR. EILEEN DUGGAN

Abstract

BACKGROUND: Type II Diabetes Mellitus is a common disease associated with multiple debilitating symptoms, including reduced fertility in women of reproductive age. Gut hormone therapies have shown promise in improving fertility in these patients.

OBJECTIVES:

1. To identify the relationship between the human gut microbiota and the successful functioning of the female reproductive system.
2. To explore treatments to improve bacteria culture in the gut, and to examine if these improvements affect fertility in female patients with Type II Diabetes.

METHODS: A systematic search was undertaken; studies were collected from PubMed and The Diabetology and Metabolic Syndrome Journal. Searches were performed between January 2023 and March 2023. Studies focused on female patients suffering simultaneously from Type II Diabetes Mellitus and fertility complications. Ten papers that met criteria were appraised and included.

RESULTS: There is evidence to suggest a causative relationship between the gut microbiome and reproductive functioning. Infertile patients had increased abundance of the phylum Verrucomicrobia and Phascolarctobacterium in the gastrointestinal tract, and decreased amounts of genera Stenotrophomonas, Streptococcus, and Roseburia. These abnormalities were associated with depleted circulating oestrogen concentrations, irregular menstrual cycling, and hyperandrogenism.

Evidence authenticates the use of probiotics and hormone therapy in treatment of Type II Diabetes and its associated symptoms. Supplements studied included metformin, GIP agonists, and GLP-1 receptors. Across studies, patients showed significant improvements in Type II Diabetes management following treatment.

CONCLUSION: Alterations to the composition of the gut microbiome are associated with improvements in glycaemic control as well as improvements in fertility in female patients with Type II Diabetes Mellitus.

Introduction

Type II Diabetes Mellitus is an impactful disease that currently affects 537 million adults globally (Diabetes Ireland, n.d.). The disease is characterised by the pancreas producing an insufficient quantity of insulin, or the body's inability to utilise insulin (Diabetes Ireland, n.d.). Complications associated with Type II Diabetes include kidney disease, neuropathy, and infertility (Diabetes Ireland, n.d.; Diabetes.co.uk, 2023). Previously, the majority of female patients with Type II Diabetes were postmenopausal, which severely limited research surrounding reproductive effects of the disease (Livshits and Seidman, 2009). However, with rapidly increasing Type II Diabetes rates, greater proportions of younger patients are suffering from this disease. The current prevalence of Type II Diabetes in women of reproductive ages ranges from 3% to 7% (Williams and Kreider, 2021), with the World Health Organization defining "reproductive age" as 15-49 years old (World Health Organization, n.d.). The reduction in the mean age of Type II

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Diabetes Mellitus patients is presenting new challenges in the disease's management. Adverse effects on fertility in female patients is a growing and substantial concern. Available studies show women with Type II Diabetes have a higher rate of both infertility and miscarriage than the general population (Mattsson et al., 2021). Women suffering from Type II Diabetes furthermore have a higher prevalence of oligomenorrhea, irregular menses, and diminished ovarian reserve, and are at higher risk for pregnancy loss than their undiagnosed counterparts (Mattsson et al., 2021).

Bariatric surgery is the leading option to improve fertility in Type II Diabetes patients (Cheah et al., 2022). The term, "bariatric surgery" encompasses a number of operations that promote weight loss by altering the digestive system (Mayo Clinic, 2023). Bariatric surgery is associated with a reduction in insulin resistance, hyperandrogenism, menstrual irregularity, and ovulatory dysfunction (Lee et al., 2020). There are strict requirements to undergo bariatric surgery, including a patient BMI greater than 40 kg/m2 (NHS, 2024). The overarching benefit of this surgery on fertility is the restoration of normal reproductive hormone levels (Moxthe et al., 2020). The gut microbiota interacts with a number of reproductive hormones including oestrogen and testosterone (Qi et al., 2021); new oral supplementation therapies have the potential to mitigate the effects of Type II Diabetes on female fertility in women who are unable or unwilling to undergo bariatric surgery. While available research is minimal, promising results have already appeared in clinical trials, chart reviews, and systematic literature reviews.

Objectives

The objective of this literature review is to systematically examine scientific databases to identify and analyse published scientific literature pertaining to:

1. The relationship between the human gut microbiota and the successful functioning of the female reproductive system regarding successful implantation and delivery.
2. The therapeutic use of hormonal medications and dietary probiotics to improve the culture of bacteria in the gut, and the effect these therapies have on fertility in female patients with Type II Diabetes.

Methodology

SEARCH STRATEGY

An electronic database search was conducted using PubMed and The Diabetes and Metabolic Syndrome Journal. Search strategy was devised to yield case-control studies, retrospective chart reviews, and systematic literature reviews that addressed the objectives of this review.

The following search strategy was used for PubMed:

I. ((Gut Microbiota) OR (Gut Microbiome) OR (GIP) OR (GLP-1) OR (Gut Hormones) OR (Probiotics))

AND

II. ((Infertility) OR (Reproductive Function) OR (Menstrual Irregularities) OR (Glycaemic Control) OR (Reproduction) OR (Oestrogen))

Filters applied: Clinical Trial, Meta-Analysis, Randomised Controlled Trial, Systematic Review, Female

Using the above key words without applying filters initially yielded 755 results. Results were filtered to exclusively include studies conducted between 2010 and 2022 and studies available in their free full text, yielding 335 records. This temporal limitation was applied to prioritise the inclusion of recent and significant studies. Additionally, gender and age filters were applied to narrow studies to females between 13-49 years of age, yielding 234 studies. Subsequently, a title screening process was conducted, involving the examination of titles and abstracts to eliminate clearly irrelevant material. This screening led to the exclusion of an additional 207 studies, leaving 34 records for further appraisal. From these, 24 records were excluded due to failing to meet the predefined inclusion/exclusion criteria or not appropriately addressing the stated objectives. Detailed inclusion/exclusion criteria are presented in Table 1. 8 records in total were selected for review and appraisal.

The following search strategy was used for The Diabetes and Metabolic Syndrome Journal:

I. "Probiotic"

AND
II. “Type II Diabetes”
AND
III. “Hormone”
AND
IV. “Management” OR “Treatment” OR “Therapy”

Using the above key words yielded 8 records. 4 of these records were duplicates of the systematic search conducted with PubMed. The remaining four studies were screened and two were selected for review and appraisal. The study selection process is illustrated in a PRISMA Flow Diagram in Figure 1.

SELECTION CRITERIA

Table 1: inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Studies available in English	Studies using exclusively male populations
Studies conducted between 2010 - 2022 inclusive	Narrative literature reviews, editorials, or periodicals
Case-control studies, retrospective chart reviews, and systematic literature reviews	Studies exploring gut hormone therapy to treat infertility caused by Type I Diabetes Mellitus or obesity, without specific reference to Type II Diabetes Mellitus
Peer-reviewed studies published in academic journals	Studies unavailable in English
Human trials and animal trials	Studies without full text availability
Studies exploring the link between Type II Diabetes Mellitus and infertility, with reference to treatment methods	Studies that exclusively addressed delay of menarche as a marker of fertility, without addressing presentation in later life
Studies exploring treatment methods to infertility, with reference to the involvement of Type II Diabetes Mellitus	

SELECTION PROCESS

When evaluating case-control studies, both human and animal trials were included in the final review. This is due to the contemporary nature of research in this field. Initial attempts to exclusively include trials with human subjects severely limited results.

To expand the scope of accessed articles while ensuring relevance, two search engines were explored. The two articles yielded from the search of The Diabetes and Metabolic Syndrome Journal were not published in PubMed. Due to the specialised nature of The Diabetes and Metabolic Syndrome Journal, the search strategy employed for PubMed had to be modified to yield relevant results from The Diabetes and Metabolic Syndrome Journal.

Due to the range of key terms associated with this area of research, narrowing search terms without excluding relevant literature proved challenging. To ameliorate this, three records were selected from the references section of records obtained from this systematic search. These studies addressed the objectives of this systematic review and met all relevant selection criteria.

All records were appraised prior to inclusion to ensure the quality of the studies. Analysis of all records was performed using The Critical Appraisal Skills Programme (CASP) Checklist for their respective genre of publication. CASP Analysis of the included articles is detailed in Table 4 (Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Salles, Cioffi and Ferreira, 2020; Jensterle et al., 2019; Shyangdan et al., 2010; Rittiphairoj et al., 2020), Table 5 (Komiya et al., 2020; Khalili et al., 2019; Khan et al., 2022; Rosenstock et al., 2021), and Table 6 (Christ and Falcone, 2018).

Results

Ten records were selected and appraised, including four case-control studies, five systematic review studies, and one retrospective chart review. Locations of studies included Japan, the United States, and Ireland. Of the case-control studies, sample sizes ranged from 36 to 478. A number of key themes emerged: significant differences existed between the gut microbiota of female patients with Type II Diabetes Mellitus and the control population. Studies furthermore demonstrated that restoration of the gut microbiota to standard conditions aided in primary management of T2DM, as well as management of symptoms, including infertility. A summation of included studies is detailed in Table 3. Abbreviations used in Table 3 are detailed in Table 2.

Objective 1: To explore the relationship between the human gut microbiota and the successful functioning of the female reproductive system in regard to successful implantation and delivery.

The relationship between bacteria population in the human gastrointestinal tract and infertility rates is primarily investigated in five of the included studies (Komiya et al., 2020; Khan et al., 2022; Christ and Falcone, 2018; Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Jensterle et al., 2019). Significant differences were found between the gut microbiome makeup of

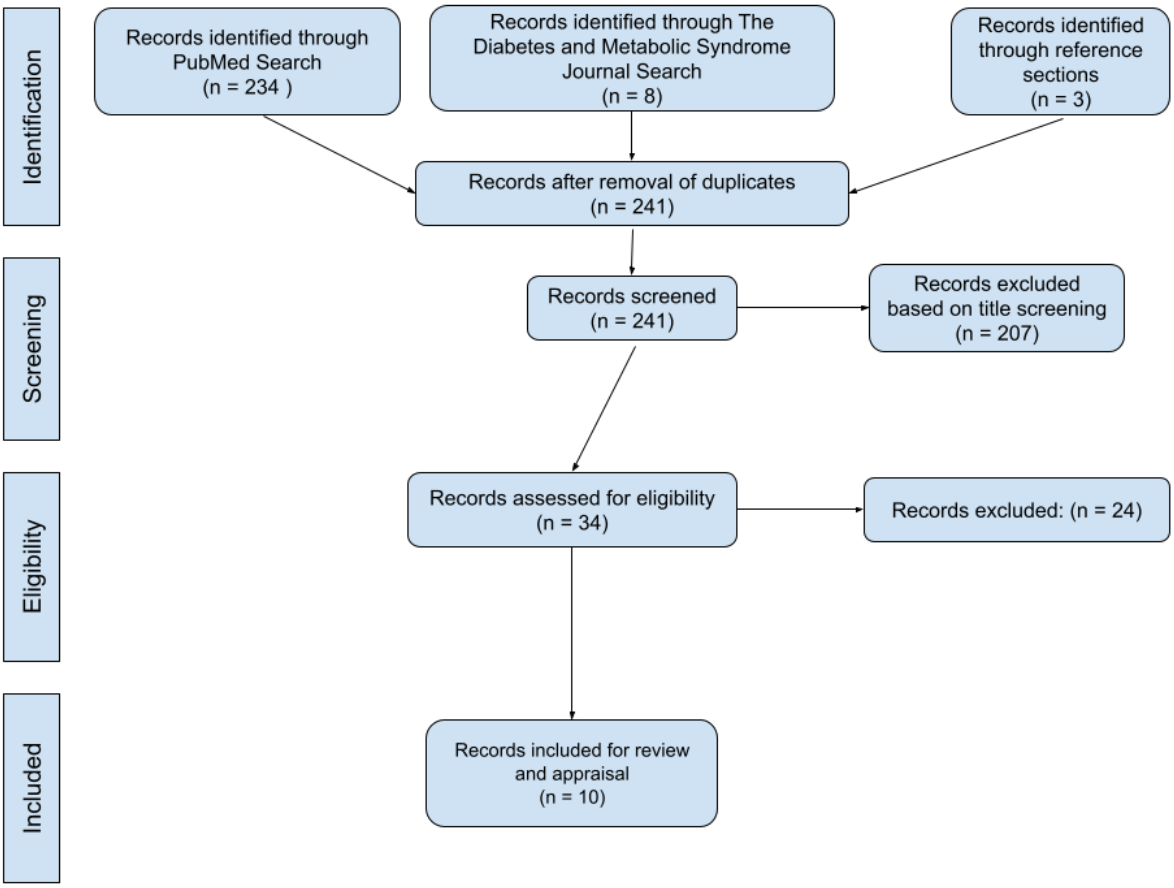

Figure 1: Flow chart illustrating study selection process.

Table 2: List of abbreviations present in Table 3

Abbreviation	**Full meaning**
BMI	Body Mass Index
PHGG	Partially Hydrolyzed Guar Gum
T1D	Type I Diabetes
T2DM	Type II Diabetes Mellitus
CFU	Colony Forming Unit
L. Casei	Lactobacillus Casei
fetuin-A	Alpha-2-HS-Glycoprotein
$SIRT_1$	Nicotinamide Adenosine Dinucleotide (NAD)-Dependent Deacetylase Sirtuin-1
HbA1c	Glycohemoglobin
PYY	Peptide Tyrosine
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide 1
GLP-1R	Glucagon-Like Peptide 1 Receptor
PCOS	Polycystic Ovary Syndrome
FBG	Fasting Blood Sugar

Table 3: Summaries of articles selected for inclusion.

Author, date, location, title	**Objective**	**Study Type, Population, sample size**	**Methodology**	**Key Findings**	**Strengths and weaknesses**
Komiya et al. (2020), Japan Characterising the gut microbiota in females with infertility and preliminary results of a water-soluble dietary fibre intervention study	To contrast the gut microbiota in infertile female patients to that in fertile control subjects. To examine the effect of prebiotic partially hydrolyzed guar gum supplementation on the outcomes of fertilisation attempts in these infertile patients.	Case-control study Population: 18 women with infertility and 18 fertile controls. No significant variation in BMI, age, or diet. Sample size = 36	Prior to experiment, faecal samples were obtained, and a microbiome analysis was performed. Observed species and differences in microbiomes between control and experimental subjects were noted. 12 of the 18 infertile subjects received PHGG supplementation while undergoing embryo transfer.	Not insignificant differences were found between the gut microbiomes of the control and experimental groups prior to experimentation. PHGG supplementation aided to homogenise the gut microbiota of infertile patients to that of the control group. 58.3% of infertile participants became pregnant and carried to term.	<u>Strengths</u>: Adequate elimination of secondary factors between participants Sampling technique was standardised <u>Weaknesses</u>: Conflict of interest: funding from EA Pharma Co. LTD to support this study Small sample size
Khalili et al. (2019), Tabriz, Islamic Republic of Islam The Effects of Lactobacillus casei on Glycemic Response, Serum Sirtuin1 and Fetuin-A Levels in Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Trial	To evaluate the effect of Lactobacillus Casei 01 dietary supplementation on diet, body weight, and glycemic control in patients with T2DM.	Case-control study Population: patients with T2DM, 30-50 years of age, BMI < 35 kg/m^2, patients were diagnosed with T2DM for at least one year. Exclusion criteria: patients with thyroid disorders, immunodeficiency diseases, and patients who had used alternative probiotic products within previous two months prior to testing. Sample size = 40	40 patients with T2DM were separated into two groups. One group received a daily probiotic containing 10^8 CFU/ml of L. casei 01 for 8 weeks. The secondary control group consumed placebo capsules containing maltodextrin for 8 weeks. Participants' dietary intake, anthropometric measurements, and hormonal levels were assessed at the beginning and the end of this eight-week period.	Patients consuming probiotic L. casei 01 supplements significantly reduced caloric intake compared to placebo. At the end of the 8-week period, the experimental group had improved fetuin-A levels, $SIRT_1$ levels, and glycaemic response compared to the control group.	<u>Strengths</u>: Double-blind, placebo controlled Sampling technique was standardised <u>Weaknesses</u>: Experiment fails to directly address effects of treatment on the reproductive system, only analyses effects on hormone levels

Table 3 continued

Khan et al. (2022) Ulster, United Kingdom Evidence for Involvement of GIP and GLP-1 Receptors and the Gut-Gonadal Axis in Regulating Female Reproductive Function in Mice	To evaluate the role of GIP and GLP-1 receptors in reproductive functioning. To examine how the presence or absence of these receptors affects oestrous cycling in mice.	Case-control study 14-week-old female mice bred at Ulster University Animal Unit. Body weight, non-fasted blood glucose levels, and insulin levels of control mice and experimental mice showed no significant variation. Sample size = N/A	Vaginal sampling was conducted to obtain information regarding oestrous cycling in female mice prior to experimentation. Samples were collected and examined over a twenty-day period. GIPR -/- Mice, GLP-1 Receptor -/- Mice, and Wild Type Mice underwent 3 breeding periods of 21 days. Following the 1st breeding period, all mice were treated with oral metformin prior to the subsequent two breeding periods.	Female mice deficient in GIP and GLP-1 gut hormones had significantly different oestrous cycling compared to control mice. Fewer of these deficient mice were capable of breeding with wild type male mice across three breeding cycles. Mice capable of breeding had significantly smaller litters than the wild type of control mice. Supplementation with oral metformin significantly improved litter size in female mice. Supplementation was not associated with improvements in pregnancy outcomes.	<u>Strengths</u>: Strong correlation between gut hormone levels and reproductive functioning Sampling technique was standardised <u>Weaknesses</u>: Animal-based study; limited extrapolation to human species No provided sample size, only percentages given in results. Challenging to assess validity of results
Christ et al. (2018), Ohio, United States Bariatric Surgery Improves Hyperandrogenism, Menstrual Irregularities, and Metabolic Dysfunction Among Women with Polycystic Ovary Syndrome (PCOS)	To characterise the ability of bariatric surgery to improve fertility in patients with PCOS.	Retrospective chart review 930 women who had undergone bariatric surgery from 2009-2014 inclusive. 44 women with PCOS and 63 controls were chosen.	Evaluations were done of pre-operative and post-operative menstrual regularity, ovarian volume, and BMI measurements in bariatric surgery patients. Further analysis of reproductive hormones, lipid imbalance, and blood sugar levels was performed.	Bariatric surgery led to significant reduction in androgen levels, hyperandrogenism, and irregular menstrual cycling. Study suggests a strong correlation between bariatric surgery and improved fertility amongst female patients.	<u>Strengths</u>: Large sample size <u>Weaknesses</u>: Secondary variable: unable to distinguish if improved fertility is due to weight loss or hormonal influences

Table 3 continued

Rosenstock et al. (2021), multicentre Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with Type II Diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial	To examine the use of GIP hormones and GLP-1 Receptors in the treatment of T2DM and its secondary effects. To evaluate the side effects of gut hormone therapy, and to question if it is comparable to dietary and exercise regime changes.	Placebo-control study Adult participants with T2DM. HbA1c ≥ 7·0% to ≤ 9·5%. BMI ≥ 23 kg/m^2. Participants had a stable weight (no change ≥ 5%) during the previous 3 months. Participants agreed to not alter diet or exercise habits during the study with the intent of reducing body weight. Exclusion criteria: included patients with T1D and use of any oral antihyperglycemic medication for 3 months prior to screening. N = 478	Parallel group trials were conducted in four countries across 52 research centres. Following a 3-week screening period, Patients underwent 40 weeks of tirzepatide treatment, followed by a 4-week follow-up period. Patients were given tirzepatide in escalating doses, 15mg dosage was achieved at 20 weeks. Patients were randomly assigned to receive a placebo, or a once weekly oral dose of 15mg tirzepatide.	Participants receiving hormone therapy had significantly improved glycaemic control compared to the placebo group. Experimental group also experienced a reduction in body weight and had no increased risk of hypoglycaemia.	<u>Strengths</u>: random sampling Large sample size Double-blind, placebo controlled Patients were thoroughly examined before and after receiving supplementation <u>Weaknesses</u>: Study does not distinguish effects on female patients from male patients
Baker et al. (2017), Arizona, United States Oestrogen-gut microbiome axis: Physiological and clinical implications	To contemplate a number of oestrogen-modulated diseases, and how they are impacted by the gut microbiota. To examine treatment options for reproductive complications caused by metabolic diseases, including T2DM.	A systematic review Inclusion criteria: search terms included “Oestrogen and Gut Microbiome”, “Metabolic Syndrome”, and “Infertility”. No limitations were applied to publication dates.	Search using PubMed and Google Scholar databases to collect scientific literature. All included studies were manually examined for relevance to the topic.	Decreased microbial diversity in the gut microbiome is strongly associated with decreased circulating oestrogen concentrations. Lowered circulating oestrogen concentrations inhibit fertility. Oral supplementation with probiotics is shown to reduce the effects of multiple metabolic syndromes, including T2DM.	<u>Strengths</u>: Extensive range of sources provided <u>Weaknesses</u>: No limitations on publication dates, possible outdated material

Table 3 continued

Salles et al. (2020), São Paulo, Brazil Probiotics supplementation and insulin resistance: a systematic review	To research the role of probiotics on markers of insulin resistance in both human and animal trials.	Systematic Review 34 probiotic intervention trials included. Inclusion Criteria: Original research articles published January 1990 - January 2020 inclusive. Search terms included "Probiotics", "Gastrointestinal Microbiome", and "Type II Diabetes".	Review based on PRISMA guidelines Two independent reviewers analysed records that met inclusion/exclusion criteria. Double entry was used to ensure accuracy of all data.	In 79% of included articles, probiotic intervention was correlated with significant beneficial alterations to insulin resistance markers. In these trials additional improvements in inflammation and gut microbiota composition were associated with probiotic supplementation. In 15% of included articles, one of the defined markers of insulin resistance improved upon probiotic supplementation. In two remaining trials, no change between control and study was detected.	<u>Strengths</u>: Objective methodology and assurances of accurate information Comparisons were made between various probiotic supplementations, probiotic supplementation under varying time periods, and probiotics compared to antidiabetic agents. Increases relevance of findings <u>Weaknesses</u>: Lack of direct research related to reproductive functioning Review contained insufficient human trials to effectively advocate for probiotic treatment
Jensterle et al. (2019) Ljubljana, Slovenia The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective	To perform an in-depth examination of the relationship between GLP-1 receptor agonists and reproductive functioning. To consider therapeutic uses of GLP-1 receptor agonists to treat infertility, especially as it is related to T2DM and obesity.	Systematic Review Inclusion criteria: search terms included "GLP-1", "GLP-1R" combined with terms including "Fertility" and "Reproductive axis", no limitations were placed on publication years. All articles were screened for relevance.	Series of PubMed data searches. Identified 983 potentially relevant pieces. Through considerate screening, final review included 6 observational studies, 24 interventional reports, 4 case reports, 1 systematic review, and 2 narrative reviews. Material was supplemented by authors' knowledge and research experience.	GLP-1 hormones seem to have anti-inflammatory and anti-fibrotic effects in the endometrium. Increased levels of these hormones mitigate damage to the endometrium associated with T2DM and obesity. Ovulation rate and menstrual frequency are consistently improved in studies where patients are treated with GLP-1 receptor agonists including exenatide and liraglutide.	<u>Strengths</u>: A highly experienced reviewer was consulted during the screening process to choose relevant studies for inclusion <u>Weaknesses</u>: Multiple underdeveloped concepts due to lack of research in contemporary areas No limitations on publication years applied

Table 3 continued

Shyangdan et al. (2010) Aberdeen, Scotland Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis	To provide evidence for the effectiveness of GLP-1 agonists in treatment and management of T2DM. To contrast the performance of GLP-1 agonists as a medication with common oral glucose-lowering drugs.	Systematic Review 28 randomised control trials were included. Studies compared GLP-1 agonists to placebos or other glucose-lowering agents. Patient population: patients with T2DM suffering from inadequate glucose control on a single oral agent or on dual therapy.	Scientific literature databases, including Medline, Embase, and the Cochrane Library and Web of Science, were searched. Three authors examined potential studies for relevance. Differences in opinion were resolved by a third party. Inclusion criteria: randomised control trials of patients with T2DM, studies conducted in full, studies conducted over a minimum duration of 8 weeks. Exclusion criteria: GLP-1 agonists used as the singular form of therapy in patients with T2DM.	All GLP-1 agonists reduced HbA1c by about 1% compared to placebo. Different agonists showed different levels of effectiveness in reducing HbA1c. Exenatide and liraglutide showed the greatest reductions in HbA1c and the greatest proportion of weight loss in patients with T2DM across trials. Most common adverse effects of GLP-1 agonists were nausea and vomiting during the early experimental period.	Strengths: Only included studies comparing GLP-1 agonists to other treatment options Thorough selection process of included studies Weaknesses: No direct link on reproductive functioning examined
Rittiphairoj et al. (2021), Maryland, United States Probiotics Contribute to Glycaemic Control in Patients with Type II Diabetes Mellitus: A Systematic Review and Meta-Analysis	To assess the effectiveness of probiotics as a management option for patients with T2DM over short- and long-term time frames. To explore differing effects of variables on probiotic treatment; variables included secondary, simultaneous, treatment plans, such as insulin therapy.	Systematic Review 26 trials were included in meta-analysis (1947 participants) Inclusion criteria: included studies that compared probiotics to placebo, comparative probiotics, or no intervention. Exclusion criteria: included studies that provided insufficient data and studies that did not address T2DM or prediabetes patients.	A search was performed using the scientific databases PubMed, Embase, and Cochrane. Trials conducted between January 2011 and February 2019 were included in the final paper. All included articles were randomised controlled trials performed with participants with prediabetes or T2DM. Two reviewers screened potential studies and assessed risk of bias using “Cochrane Risk of Bias 2”.	Probiotics reduced FBG more than the placebo/no intervention group with an average difference of –12.99 mg/dL in the short-term and –2.99 mg/dL in the long-term. There is evidence for reduced HbA1c both in short-term and long-term studies under probiotic supplementation. Effects were stronger in participants not undergoing insulin therapy.	Strengths: Steps were taken to reduce bias, including Cochrane Risk of Bias 2 Systematic review was registered with International Prospective Register of Systematic Reviews and a pre-established protocol was followed when conducting the review Large sample size Weaknesses: Unclear distinguishing between effects of various strains of probiotics.

Table 4: CASP Checklist Findings for Systematic Reviews

	Is a clearly focused question addressed ?	Are all included papers appropriate ?	Are all relevant studies included ?	Was the author's assessment of study quality sufficiently rigorous?	Was the author's method of combining results from studies valid?	What are the results of the systematic review?	Are the results sufficiently precise?	Can results be applied to the target population ?	Were all important outcomes considered ?	Do the benefits of this review outweigh the costs?
Baker et al. (2017)	Yes	Yes	Yes	No	Yes	See Table 3	Yes	Yes	Yes	Yes
Salles et al. (2020)	Yes	Yes	Yes	Yes	Yes	See Table 3	Yes	No	Yes	Yes
Jensterle et al. (2019)	Yes	Yes	Yes	No	Yes	See Table 3	Yes	Yes	No	Yes
Shyangdan et al. (2010)	Yes	Yes	Yes	Yes	Yes	See Table 3	Yes	Yes	Yes	Yes
Rittiphairoj et al. (2021)	Yes	Yes	Yes	Yes	Yes	See Table 3	No	Yes	Yes	Yes

Table 5: CASP Checklist Findings for Case-Control Studies

	Does the study address a clear objective?	Is appro-priate meth-odology used to assess the objective?	Were cases selected in an accep-table manner ?	Were controls selected in an accept-able manner?	Were measures taken to minimise bias?	Were second-ary variables between groups controlled?	Have authors included confoun-ding factors in their analysis ?	How large was the treatment effect?	How precise was the estimate of treatment effect?	Overall , are the results of the study trust-worthy ?	Can results be applied to the target popula - tion?	Do the results of this study correlate to other available evidence?
Komiya et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No	See Table 3	See Table 3	Yes	Yes	Yes
Khalili et al. (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	See Table 3	See Table 3	Yes	No	Yes
Khan et al. (2022)	Yes	Yes	Yes	Yes	Yes	Yes	No	See Table 3	See Table 3	Yes	No	Yes
Rosenstock et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	See Table 3	See Table 3	Yes	Yes	Yes

Table 6: CASP Checklist Findings for Cohort Studies

	Does the study address a clearly focused issue?	Was the Cohort recruited in an acceptable manner?	Was exposure measured to minimise bias?	Were outcomes measured to minimise bias?	Have confound-ing factors been identified and analysed?	Was the follow up of subjects sufficiently long and accurate?	What are the results of this study?	How precise are the results of this study?	Overall, are the results of the study trustworthy?	Can results be applied to the target population?	Do the results of this study correlate to other available evidence?
Christ et al. (2018)	Yes	Yes	Yes	Yes	No	Yes	See Table 3	See Table 3	Yes	No	Yes

female patients with normal and impaired reproductive function. Depleted circulating oestrogen concentrations, irregular menstrual cycling, hyperandrogenism, and endometrium tissue damage were all used as markers of diminished fertility.

Komiya found infertile patients had increased abundance of the phylum Verrucomicrobia, the genera Unclassified [Barnesiellaceae], and Phascolarctobacterium. The gut microbiome of infertile women is furthermore more likely to contain a decreased amount of the genera Stenotrophomonas, Streptococcus, and Roseburia (Komiya et al., 2020). Baker's systematic review found increased diversity is related to improved fertility via increased circulating oestrogen concentrations (Baker, Al-Nakkash and Herbst-Kralovetz, 2017).

Khan's case-control study explored the effects of GIP and GLP-1 Hormones on reproductive functioning. This trial found mice with diminished amounts of GIP receptors and GLP-1 receptors had significantly ($p < 0.05$ and $p < 0.01$) deranged oestrous cycling compared to control mice. These mice furthermore produced significantly fewer litters than wild type mice, and litters produced were notably smaller ($p < 0.001$ - $p < 0.05$) than control litters. However, there were no differences in pregnancy outcomes between control and experimental mice (Khan et al., 2022). Jensterle corroborated these findings, using endometrium inflammation and fibrosis as principal measures of infertility (Jensterle et al., 2019).

It has been well established in alternative studies that bariatric surgery alters hormone concentrations in the gut microbiome (Ulker and Yildiran, 2019). Christ explored the effects of bariatric surgery on fertility rates in previously infertile patients. Surgery led to significant reduction in androgen levels, hyperandrogenism, and irregular menstrual cycling (Christ and Falcone, 2018).

Objective 2: To consider the therapeutic use of hormonal medications and dietary probiotics to improve the culture of bacteria in the gut, and to explore the effect these therapies have on symptom management in patients with Type II Diabetes, with a special focus on fertility.

Nine of the included studies addressed treatment options for Type II Diabetes Mellitus and associated infertility, with focus on the human gut microbiome (Komiya et al., 2020; Khalili et al., 2019; Khan et al., 2022; Rosenstock et al., 2021; Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Salles, Cioffi and Ferreira, 2020; Jensterle et al., 2019; Shyangdan et al., 2010; Rittiphairoj et al., 2020).

Through dietary fibre supplementation, Komiya's case-control study shows a normal gut microbiome may be re-established in patients with T2DM. Following supplementation, infertile patients underwent embryo transfer, where 58.3% had successful pregnancies. Successful patients demonstrated a significant decrease in Paraprevotella and Blautia levels and an increase in the abundance of Bifidobacterium (Komiya et al., 2020).

Khalili studied effects of Lactobacillus casei 01 supplementation on symptoms in T2DM patients. Following treatment, patients had significantly decreased serum fetuin-A level, insulin concentrations, insulin resistance, and fasting blood sugar. These patients furthermore had increased serum SIRT1 levels (Khalili et al., 2019). These results were corroborated by Rittiphairoj's systematic review (Rittiphairoj et al., 2020). Lactobacillus was additionally studied in Salles's systematic review. Salles's results corroborated Khalli's

findings, with patients receiving supplementation showing improved lipid profile, inflammatory and oxidative markers, short-chain fatty acid production and gut microbiota composition (Salles, Cioffi and Ferreira, 2020). Finally, Rittiphairoj examined Lactobacillus as a treatment option for T2DM patients. Supplementation resulted in reduced fasting blood glucose compared to the placebo group with an average difference of –12.99 mg/dL in the short-term and –2.99 mg/dL in the long-term (Rittiphairoj et al., 2020).

Two included studies explored the effect of metformin, a drug treatment used to restore hormone levels in the body, on infertility caused by T2DM (Khan et al., 2022; Baker, Al-Nakkash and Herbst-Kralovetz, 2017). In mice trials conducted by Khan, metformin increased litter size (approximate 100% increase in litter size) (Khan et al., 2022). Baker's study furthermore showed Metformin alters the gut microbiome by increasing Akkermansia levels (Baker, Al-Nakkash and Herbst-Kralovetz, 2017).

A number of included studies explored the effects of GIP and GLP-1 receptors and agonists on glycaemic control and reproductive functioning in T2DM patients. Rosenstock explored this phenomenon through tirzepadide supplementation over a 40-week trial period. Patients receiving 15mg supplementation experienced a reduction in mean HBA1c by 2.07% (compared to placebo group HBA1c, which showed an increase of 0.04%). Furthermore, 31-52% of patients on tirzepatide achieved HbA1c of less than 5·7%, compared to 1% of patients receiving placebo supplementation (Rosenstock et al., 2021). Shyangdan corroborated these findings; their systematic review showed a range of GLP-1 agonists reduced HbA1c by about 1% compared to placebo administration in T2DM patients (Shyangdan et al., 2010). Jensterle's systematic review had similar findings; patients treated with GLP-1 receptors showed improved ovulation rate and menstrual frequency (Jensterle et al., 2019). Specifically, both Jensterle's and Shyangdan's systematic reviews examined the effects of exenatide and liraglutide GLP-1 receptor agonists on general T2DM management (Shyangdan et al., 2010), as well as direct effects on reproductive functioning (Jensterle et al., 2019). Both articles found significant improvements in markers of T2DM, as well as symptom management (Jensterle et al., 2019; Shyangdan et al., 2010).

Discussion

This systematic review consisting of ten studies aims to analyse the relationship between the gut microbiome and Type II Diabetes, with a focus on treatment options of female infertility through manipulation of this relationship. There is evidence suggesting a correlation between the gut microbiome and the reproductive capacity of female patients with T2DM (Komiya et al., 2020; Khan et al., 2022; Christ and Falcone, 2018; Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Jensterle et al., 2019). Furthermore, a number of successful trials demonstrated an association between various gut therapies and improvements to reproductive capabilities (Komiya et al., 2020; Khalili et al., 2019; Khan et al., 2022; Rosenstock et al., 2021; Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Salles, Cioffi and Ferreira, 2020; Jensterle et al., 2019; Shyangdan et al., 2010; Rittiphairoj et al., 2020).

STRENGTHS OF REVIEW

Studies (Komiya et al., 2020; Khalili et al., 2019) made efforts to eliminate possible confounders. BMI, age, and years since diagnosis of T2DM were consistent between intervention and control groups. While this limits application of studies to a wider population, it largely eliminates secondary variables that could influence findings.

All included studies were conducted in a rigorous manner, with specific efforts being made to reduce bias. Sampling techniques were standardised across studies (Komiya et al., 2020; Khalili et al., 2019; Khan et al., 2022; Rosenstock et al., 2021). Placebo-controlled studies utilised double-blind testing procedure (Khalili et al., 2019; Rosenstock et al., 2021). Systematic reviews were based on strict guidelines, including PRISMA guidelines (Salles, Cioffi and Ferreira, 2020), and multiple independent reviewers screened included records to reduce possible bias (Salles, Cioffi and Ferreira, 2020; Jensterle et al., 2019; Shyangdan et al., 2010; Rittiphairoj et al., 2020). Shyangden's and Rittiphairoj's systematic reviews utilised Cochrane Collaboration's tool for risk assessment of bias (Shyangdan et al., 2010; Rittiphairoj et al., 2020).

Selection criteria of this systematic review was carefully chosen to yield a range of relevant material.

Appropriate use of key terms, filters, and inclusion and exclusion criteria was strictly adhered to. Efforts were made to reduce risk of bias, including a CASP analysis of included systematic reviews (Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Salles, Cioffi and Ferreira, 2020; Jensterle et al., 2019; Shyangdan et al., 2010; Rittiphairoj et al., 2020), case-control studies (Komiya et al., 2020; Khalili et al., 2019; Khan et al., 2022; Rosenstock et al., 2021), and retrospective chart reviews (Christ and Falcone, 2018).

LIMITATIONS OF REVIEW

This systematic review does not address the effect of BMI on treatment outcomes. Studies (Komiya et al., 2020; Khalili et al., 2019; Rosenstock et al., 2021; Rittiphairoj et al., 2020) used exclusively female patients of a healthy BMI. All chosen subjects had similar BMI (Komiya et al., 2020: fertile control BMI 20.78 ± 2.39, infertile patient BMI 21.41 ± 3.34). (Khalili et al., 2019: BMI < 35 kg/m2). (Rosenstock et al., 2021: Control BMI = 31.7, experimental BMI = 31.5), (Rittiphairoj et al., 2020: Control BMI 29.14 ± 0.78, Intervention BMI: 28.95 ± 0.67). This eliminates the secondary factor of weight on glycaemic control and fertility. However, it severely limits the applicability of these treatments on a wider population. Currently, 90% of adult patients with T2DM are overweight or obese. (Public Health England, 2014). One of the objectives of this systematic review is to evaluate treatment options for infertility caused by T2DM. Further research is required to establish the effect of obesity on treatment outcome.

The findings of some included studies addressed the relationship between metabolic syndromes, including T2DM, and the gut microbiome, without explicit reference to effects on reproductive functioning (Khalili et al., 2019; Rosenstock et al., 2021; Salles, Cioffi and Ferreira, 2020; Shyangdan et al., 2010; Rittiphairoj et al., 2020). There are alternative included studies (Komiya et al., 2020; Khan et al., 2022; Christ and Falcone, 2018; Baker, Al-Nakkash and Herbst-Kralovetz, 2017; Jensterle et al., 2019) and established scientific literature (Moxthe et al., 2020; Qi et al., 2021) that demonstrate a relationship between the gut microbiome and the female reproductive system. However, it is still extrapolation to assume probiotic and hormonal treatments that improved T2DM markers would additionally improve fertility in these patients. There are limited applications of these studies for fertility treatments for patients.

A mice-based study was included in this report (Khan et al., 2022), as well as a systematic literature review that focused on animal-based trials (Salles, Cioffi and Ferreira, 2020). Due to the novel nature of this research, inclusion of these studies was vital to provide an encompassing image of research in this field. However, there are severe limitations in applications of these results to a human population.

This systematic review was conducted by one author; this presents a risk of bias in selection and appraisal of included records. Furthermore, this systematic review was constrained by its inclusion criteria, which only included articles available in their full, free text. This inherently limits the breadth of articles included in this paper. A systematic review including restricted articles may yield additional or divergent results. To supplement the systematic review process, handsearching was undertaken. This involved scrutinising the reference lists of the included articles to identify additional case-control studies, retrospective chart reviews, and systematic literature reviews that were not captured in the original search. However, the use of handsearching compromises the integrity of this systematic review. This underscores the importance of employing flexible key terms throughout a systematic search process to ensure a comprehensive review.

Conclusion

Alterations to the hormonal and bacteria composition of the gut microbiome are associated with improvements in glycaemic control and fertility in patients. Therapeutic use of hormonal and bacterial supplementation may improve infertility caused by Type II Diabetes Mellitus in female patients. However, this is still a novel area of research, and there is a notable lack of human-based clinical trials available examining the effects of hormonal and bacterial supplementation on Type II Diabetes Mellitus and the disease's symptoms. Further research is required to clarify the link between metabolic diseases, the gut microbiome, and reproductive functioning. Once these relationships are less ambiguous, more significant progress can be made in management of this disease.

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A Two-Dimensional Cellular Automaton Model of Parasystole

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Abstract

Under normal cardiac conditions, the sinoatrial node is the pacemaking region which initiates depolarization in the heart; in parasystole, there also exists an ectopic pacemaker which may initiate depolarization waves. Parasystole is a form of arrhythmia caused by the influence of the secondary pacemaker on cardiac behaviour. Specifically, we consider cases of pure parasystole, where the two pacemakers are protected from each other. Previous theoretical models of pure parasystole consider the interaction of two pacemakers without incorporating physical space. The objective here is to create a simple, theoretical, two-dimensional model of pure parasystole where the distance between the pacemakers may be adjusted. A cellular automaton model was created using Python 3.8.3 and associated packages. The model was used to evaluate how changes in space influenced cell activation cycles and the number of intervening sinus beats (the number of times cells were activated by the sinus node versus the ectopic pacemaker). The model dynamics were further compared to experiments using optogenetic methods to stimulate a cardiac monolayer from two sites. This model provides insight into the physical dynamics of parasystole in its most basic form so that it may be built upon to eventually be used in a clinical context.

Introduction and Review of Literature

The function of the mammalian heart depends on its ability to propagate action potentials and contract synchronously. An action potential (AP) is a brief period of electrical depolarization followed by a brief period of electrical repolarization near the cellular membrane (Wei et al. 2020). Under normal physiological conditions, the sinoatrial (SA) node initiates cardiac depolarization waves to the rest of the heart (Alanís et al. 1958). As the wave propagates, the propagation speed slows down near the atrioventricular (AV) node to provide time for the atria to contract ahead of the ventricles. The AP depolarization typically lasts for 250 milliseconds and the absolute repolarization period lasts for 150 milliseconds, after which the cell is brought to rest to be excited again (Kléber & Rudy, 2004). The electrical impulse is coupled with a physical contraction, which allows the pumping of blood (Bers et al., 2002).

Parasystole is an arrhythmia where there exists a secondary pacemaker, along with the SA node, that may propagate AP waves itself. The influence of this secondary, otherwise known as ectopic, pacemaker on cardiac electrical properties can lead to arrhythmias and uneven heart contractions. Cardiac contractions from the SA node are known as sinus beats and contractions from the ectopic pacemaker are known as ectopic beats (Pick, 1953).

Parasystole was originally defined by GB Fleming (Fleming, 1912). According to Fleming, fusion beats are when both the SA node and ectopic pacemaker fire together, and the ectopic pacemaker is protected from depolarization by the sinus node (Pick, 1953). The protection of the ectopic focus is due to a surrounding region of tissue that tends to propagate waves in only one direction.

When two pacemakers can electronically influence each other, it is called modulated parasystole; when they are protected from each other, it is referred to as pure parasystole. Mathematical models of pure parasystole assume that there is no electronic influence between the pacemakers. In the theoretical

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model by Glass et al. in 1986, the authors varied the ratios between the sinus pacemaker period (S) and the ectopic pacemaker period (E), and between S and the refractory period after a sinus beat (θ) (Glass et al., 1986). During each variation they recorded the number of intervening sinus beats (NIBs) between ectopic beats and proposed the following set of rules for pure parasystole at fixed E, S and θ values:

1. There are at most three different values for the NIBs.
2. One and only one of these NIBs is odd.
3. The sum of the two smaller values is one less than the largest value.

These results allowed the authors to predict the NIBs depending on the E/S and the θ/S ratios in a dimensionless environment (Fig 1).

A consideration not made in the paper above or other models of parasystole is the distance between the pacemaking regions, which is an important feature to study because it influences the timing of dynamics. If the distance between pacemaking sites varies, we would expect to see varying NIBs.

This project aims to display the dynamics in pure parasystole when the distance between the pacemakers can be controlled. We created a two-dimensional (2D) Cellular Automaton (CA) model to run simulations on and compared the outputs of the model to the results of optogenetic experiments and data collected by theoretical models. We hypothesized that there will be differences in parasystole dynamics when the distance between the pacemaking regions changes, and we worked towards quantifying this relationship.

A CA model is a common tool to estimate the propagation of AP in neurological and cardiac cells (Mordvintsev et al. 2020). Rules to creating 2D CA models of cardiac cells are laid out in Bub, et al. 1998 (Bub et al. 1998). The 2D CA model of parasystole is a continuation of the work started by Diagne 2020, which considers the dynamics of parasystole in a one-dimensional (1D) CA model (Diagne, 2020). The 1D model concluded that when modeling pure parasystole without interpolated beats, the three NIB rules from Glass et al. 1986 are upheld at any point in space. Additionally, the NIB triplet sequence changes as one moves spatially away from the ectopic pacemaker, mirroring the sequence seen when the refractory period increases in a dimensionless model. We believe that our 2D CA model would output NIB patterns similar to those seen in the 1D model and in the theoretical Glass 1986 model. A great advantage of 2D CA models is that their outputs can be directly compared to the outputs of optogenetic experiments that use myocyte plates.

Optogenetic techniques allow us to generate two interacting pacemakers where the distance between the pacemakers and their relative periods can be adjusted. By generating cardiac monolayers of neonatal mice myocytes and virally transfecting them to express light sensitive channels, the monolayers can be stimulated to propagate APs using patterned light (Burton et al. 2015). This method allows us to change the distance between pacemakers more easily than with electrical stimulations (Van Meerwijk et al. 1984). Furthermore, this technique is less damaging to the tissues and provides better fluorescent visuals (Sepúlveda, 2020). The results of such experiments can then be compared

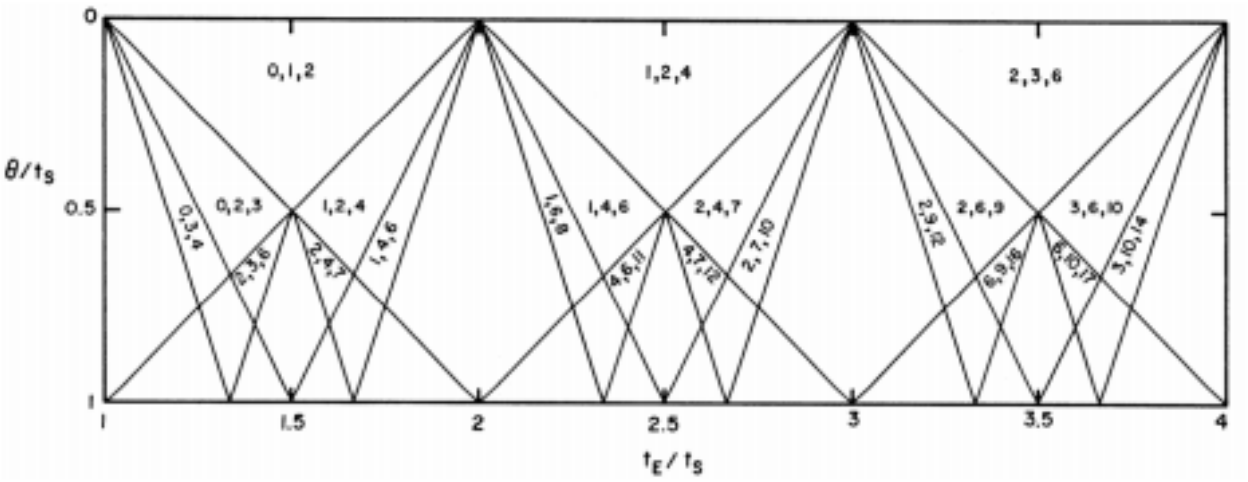

Figure 1: Allowed values of NIB depending on E/S and θ/S values. Farey diagrams of order 3. (from Glass et al. 1986)

to the results of the 2D CA simulations to ensure that the model accurately depicts cardiac behaviour.

'Simple' models of parasystole serve as a crucial foundation for comprehending arrhythmic patterns and advancing clinical interventions. These findings can pave the way for the refinement of more intricate models incorporating additional anatomical properties and parameters.

Methods and Materials

The 2D CA is run in the programming language Python 3.8.3. The Python libraries used are numpy (allows for creation and manipulation of multi-dimensional arrays), pandas (allows for large data manipulation and for creating and reading Excel files), and plotly (allows for production of interactive and high-quality graphs).

The Cellular Automaton (CA) is two-dimensional grid of discrete cells that are adjusted through time based on certain predetermined rules. Each cell in the model represents a space of 1 mm × 1 mm and each time step lasts either 1 ms or 2 ms (this will depend on what the model is representing and is explained further in the results section).

In the following work, we utilized videos of optogenetic experiments on myocyte plates that were obtained by other members of the lab (Sepúlveda, 2020).

Results

The original (first) CA model is created using methods from Bub et al. 1998 and Diagne 2020. The model consists of N × N cells where numerical states 1, 2, …, E are excitatory, E+1, E+2, …, E+R are refractory, and state 0 (also corresponding to state E+R+1) is inactive. Neighbours are the cells surrounding the cell of focus. The states are updated at every time step according to the following rules:

if $1 \leq state^t \leq E+R$:
    $state^{t+1} = state^t$
if $state^t = E+R+1$:
    $state^{t+1} = 0$

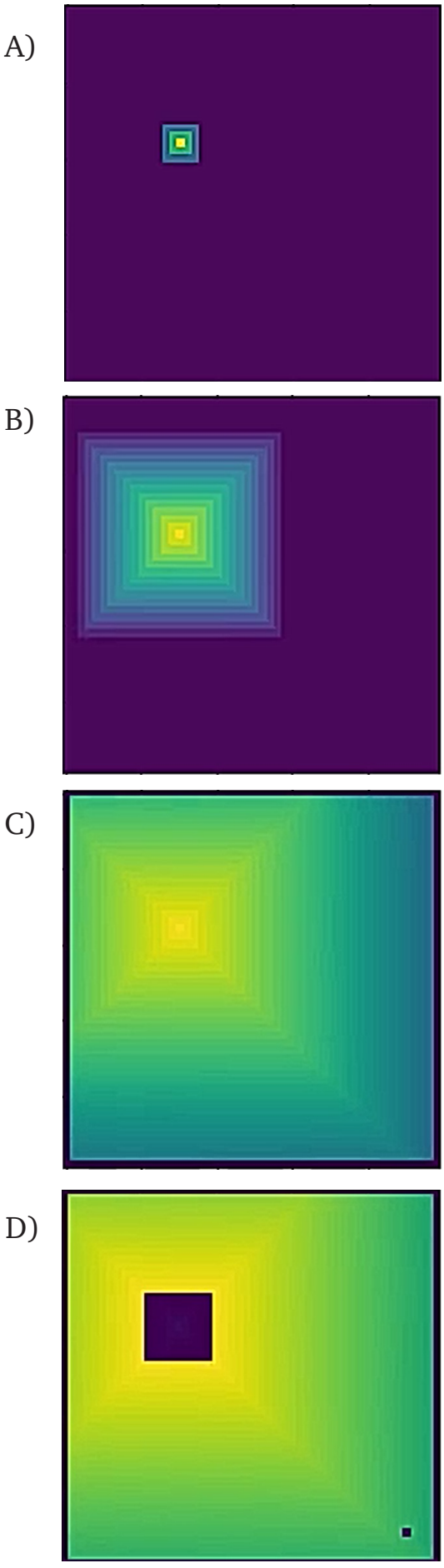

Figure 2: Images of Simulation taken with the first 2D CA Model. Parameters were ro = 50, co = 50, Period_PM1 = 160, t2 = 0, E = 90, R = 26, # neigh = 1. Sinus node was located at (18,13) and ectopic node was located at (45,45). The times taken from the video A) 1:21, B) 1:23, C) 1:31, and D) 1:37.

if $state^t = 0$:
    if $1 \leq$ neighbour $states^t \leq E$:
        $state^{t+1} = 1$
    else:
        $state^{t+1} = 0$

The neighbourhood of a cell may be the immediate cells surrounding it or can include further layers. The neighbour layers are defined in square formations. If any one of a cell's neighbours is active, the cell will become activated in the next time step. When running simulations with this model, the propagation waves appear 'square-like' and do not accurately depict cardiac behaviour (Fig 2).

The updated (second) CA model includes all the rules above except line (6) which is modified to incorporate an activation threshold and spatial heterogeneity. The modification to incorporate an activation threshold was adapted from Bub et al. 2002 (Bub et al. 2002). The model considers the number of excitatory neighbours over the total number of neighbouring cells, and if this exceeds a threshold value θ, the cell will be activated: θ is a fixed activation threshold value, typically varying between 0.20 – 0.50.

$$\frac{number\ of\ excitatory\ neighbours}{total\ number\ of\ neighbouring\ cells} \geq \theta$$

θ is a fixed activation threshold value, typically varying between 0.20 – 0.50.

We also introduce spatial heterogeneity to the second model by incorporating some randomness at the borders between influential neighbouring cells (ones that contribute more strongly to the activation of the cell) and non influential neighbouring cells. For two neighbouring cells with initial coordinates x0 and y0, the new coordinates would be x0 + x and y0 + y where x and y are randomly chosen as either –1 or 1. Based on the new coordinates, some cells immediately outside the borderline may become influential neighbours whereas some cells within the borderline may no longer be influential neighbours. When this adjustment is incorporated, the activation waves become more heterogeneous and similar to propagation waves seen in optogenetic experiments on myocyte cell plates.

The model also includes a tracker which evaluates if the cell has been activated by the ectopic or sinus pacemaker. This is used to evaluate the number of intervening beats each cell in the model experiences over time.

The input parameters of the model are:

- The number of rows in the grid (ro)
- The number of columns in the grid (co)
- The number of time steps (time_steps)
- The x and y coordinates of the sinus node (PM1x, PM1y)
- The activation period of the sinus node (Period_PM1)
- The x and y coordinates of the ectopic node (PM2x, PM2y)
- The activation period of the ectopic node (Period_PM2)
- The delay time before the ectopic node begins propagating waves (t2)
- The cell activation period of each cell (E)
- The refractory period of each cell (R)
- The number of layers of influential neighbours (# neigh)
- The activation threshold ()

Two sets of parameter choices were taken to evaluate parasystole dynamics. In the first, we took parameters that we would see on the myocyte plates. In this case, each time step is of 2 ms, and each cell represents a space of 1 mm × 1 mm. For the simulations we set ro = 100, co = 100, Period_PM1 = 160, t2 = 0, E = 90, R = 26, # neigh = 2, θ = 0.4; we then vary PM1x, PM1y, PM2x, and PM2y throughout the simulation. The value of Period_PM2 is varied with each simulation to determine how its influence will affect the NIBs along space; the ratio of the ectopic pacemaker period (Period_PM2) to the sinus pacemaker period (Period_PM1) is typically set between 1.0 – 2.0. The results from the CA simulations were then qualitatively compared to videos of myocyte plate propagations.

The visualizations created by the 2D CA model do mimic myocyte behaviour (Fig 3). We conclude from the simulations that the NIBs for the cells in the 2D CA do vary in space. These dynamics can be depicted visually, where each colour is associated with a different list of NIBs (Fig 4) (Supplementary 1). In

Figure 3: Images of Simulation taken with the second 2D CA Model. Parameters were ro = 100, co = 100, Period_PM1 = 160, Period_PM2 – 240, t2 = 0, E = 90, R = 26, # neigh = 2, θ = 0.4. Sinus node was located around (10,10) and ectopic node was located around (76,76). The times taken from the video A) 1:21, B) 1:23, C) 1:31, and D) 1:37.

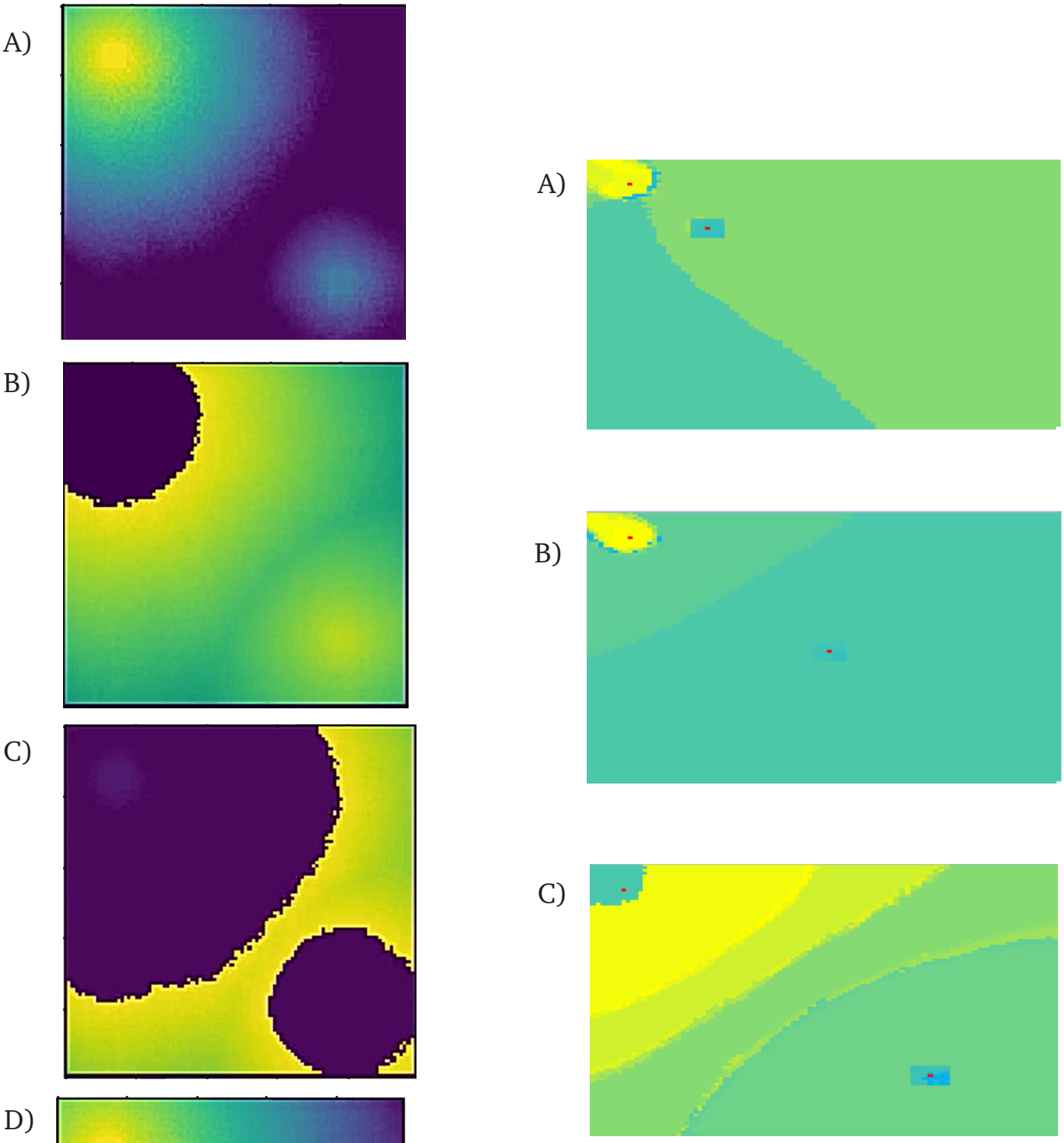

Figure 4: The NIBs data collected for simulations taken with the second 2D CA Model. Parameters were ro = 100, co = 100, Period_PM1 = 160, Period_PM2 = 240, t2 = 0, E = 90, R = 26 # neigh = 2, θ = 0.4. The sinus node was in position (10,10) and the ectopic node (shown in red) was in position: A) (26,26), B) (51,51), and C) (76,76). Each colour is associated to a different list of NIBs described in Figure 5.

these visualizations the ratio of the ectopic pacemaker period (Period_PM2) to the sinus pacemaker period (Period_PM1) is 1.5. We can also see the dividing lines between varying NIBs values. For example, the dividing line shifts dramatically from the first and second image (Fig 4.A and 4.B, respectively). This indicates that there is a critical point during which the ectopic node is between coordinates (26, 26) and (51, 51) when this dramatic shift occurs. This is an aspect that needs to be further explored in future simulations. Moreover, most of these cells typically experience more than three NIBs, meaning that they do not follow the rules set by Glass, et al 1986 (Supplementary 1). This may occur because the model does not follow the longer refractory periods found within in vivo cardiac tissue. We therefore decided to investigate a second set of parameters.

In our second set of simulations, we consider parameters that mimic the properties of cardiac cells which allow the whole heart to be activated before the beginning of a new wave of depolarization. In this case, each time step is set to 1 ms, and each cell represents a space of 1 mm × 1 mm. These simulations are compared with those in the 1D model and in the theoretical model suggested by Glass, et al 1986. We set ro = 100, co = 100, Period_PM1 = 800, t2 = 0, E = 100, R = 220, # neigh = 2, = 0.4; we then vary PM1x, PM1y, PM2x, and PM2y throughout the simulation. The value of Period_PM2 is varied with each simulation, like in the first simulation. Here the data suggests that the NIBs are not affected by the space between the nodes and for the most part, the ectopic node's dynamics are covered by the sinus node propagation. Only when the ratio between the periods is between 1.0 – 1.2 does one see small variations in the NIBs as a function of space. In these cases, the NIBs are (0, 1, 2) or (0, 1) (Fig 5), following the rules set by Glass, et al 1986 and the 1D model. Additionally, we observe that the dividing line between the different NIBs shifts by the same distance as the ectopic node does in each simulation. However, no other data matches the theoretical model, and when the ratio between periods was set above 1.5, there were no NIBs present.

Results

The data suggests that NIBs in cardiac cells are influenced by the space between the pacemaking nodes in a 2D CA Model. The simulation outcome supports the results found by Glass, et al 1986 and Diagne, 2020 when the ectopic pacemaker has a period 1.0 – 1.2 times that of the sinus pacemaker, but not otherwise. We have further shown that varying ratios for the periods of the two pacemakers in physiological ranges can also influence the overall dynamics in parasystole.

Currently, one of the model's limitations is its lack of a third dimension, meaning that it cannot entirely depict the dynamics of a 3D mammalian heart. However, we would expect to observe similar dynamics in a 3D model as we would in our 2D model. Another limitation is that the data is discrete in time, which limits the temporal resolution of the parasystole dynamics being visualized.

To advance the project and address the aforementioned limitations, we aim to develop a 3D model of pure parasystole to evaluate NIBs in three dimensions and compare this to the findings in 2D. We also plan on incorporating methods to represent time as a continuous, as opposed to discrete, variable so that it is more representative of live tissue (Ito et al. 1991). Furthermore, we aim to provide more in-depth quantitative explanations for how the space between pacemakers influences dynamics.

Conclusion

One of the original purposes of the project was to create a 2D CA model of parasystole that could be comparable to myocyte plates that have been stimulated using optogenetics. We wanted to create a model that views the impact of space upon parasystole since this is a less explored topic when determining dynamics like NIBs. Through progressive treatment, the 2D CA Model currently estimates dynamics very similar to those seen in myocyte plate recordings.

Ultimately, this project aims to quantify the dynamics observed in pure parasystole for prospective clinical applications. Although the model we propose cannot be used clinically, it may serve as a basis to build a 3D model of cardiac tissue. By beginning to understand the influence of space on parasystole, we can develop a better understanding of the physiology of parasystole.

Acknowledgments

I want to thank Dr. Gil Bub, Khady Diagne, José Miguel Romero Sepúlveda, and Thomas Michael Bury

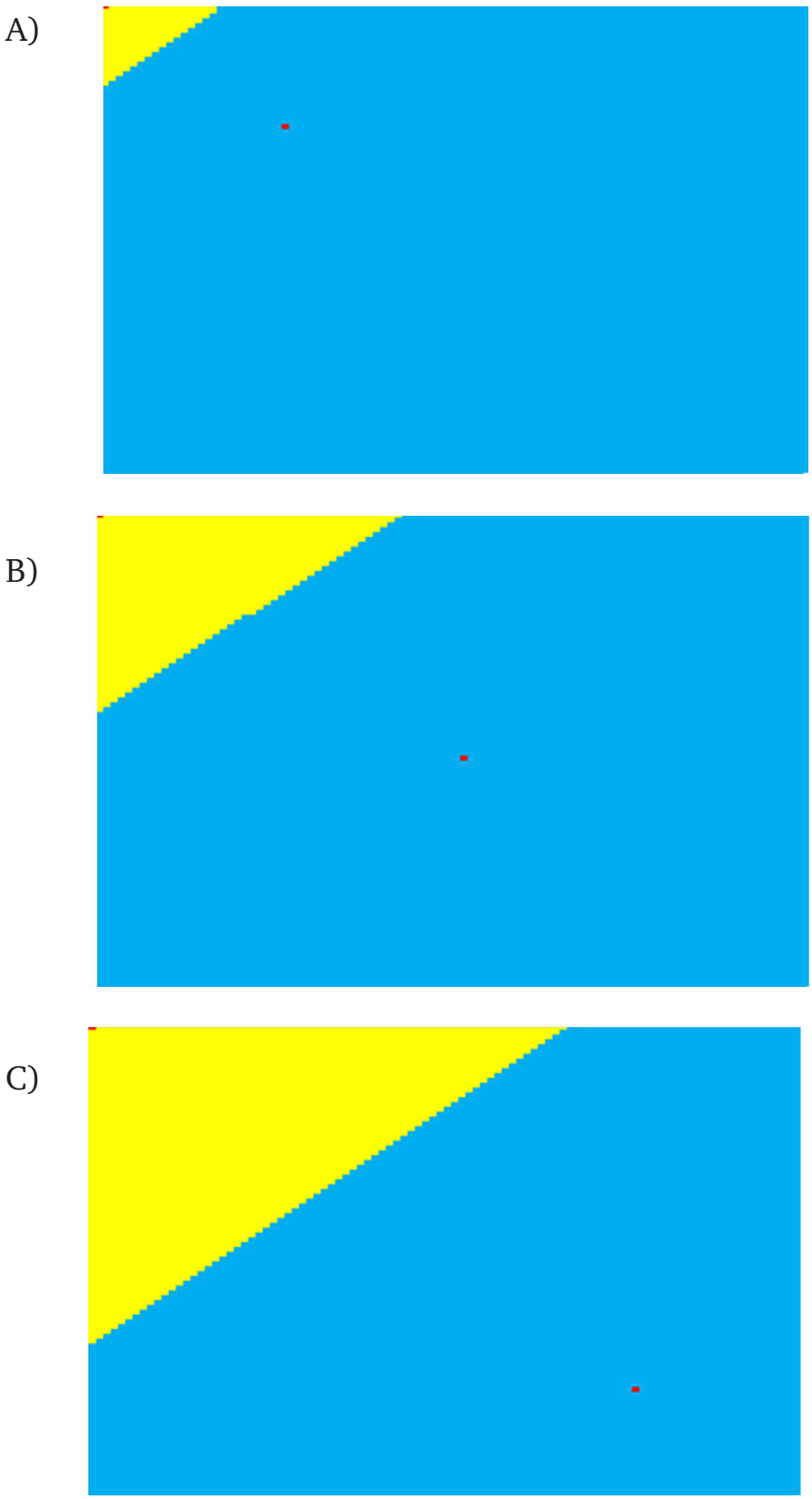

Figure 5: The NIBs data collected for simulations taken with the second 2D CA Model. Parameters were ro = 100, co = 100, Period_PM1 = 800, Period_PM2 = 960, t2 = 0, E = 100, R = 220, # neigh = 2, θ = 0.4. The sinus node was in position (10,10) and the ectopic node (shown in red) was in position: A) (26,26), B) (51,51), and C) (76,76). Yellow represents NIBs = (0,1) and blue represents NIBs = (0,1,2).

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Supplementary

1	[0, 1, 2, 3]	31	[11, 0, 3, 19, 15, 6, 4]	61	[12, 47, 11]
2	[0, 1, 2, 4, 3]	32	[11, 0, 3, 19, 15, 7, 2, 4]	62	[12, 47, 2, 0, 3]
3	[0, 1, 2]	33	[11, 0, 3, 19, 15, 7, 6, 4]	63	[12, 6, 4, 13, 7, 2, 8]
4	[0, 1, 3, 2, 4]	34	[11, 35]	64	[12, 6, 4, 2, 0, 17, 13, 7]
5	[0, 1, 3, 2, 5]	35	[12, 1, 9, 2, 0, 5, 24]	65	[15, 14, 47]
6	[0, 1, 3, 2]	36	[12, 11, 14, 8]	66	[16, 15, 47]
7	[0, 1]	37	[12, 11, 18, 6, 9, 2, 5]	67	[16, 15, 48]
8	[0, 10, 2, 13, 3, 5, 4, 1]	38	[12, 11, 25, 1, 7, 2, 8]	68	[16, 15, 49]
9	[0, 10, 2, 3, 9, 4, 1, 6]	39	[12, 11, 35, 2, 3]	69	[16, 15, 50]
10	[0, 2, 1, 3]	40	[12, 11, 35, 2, 8]	70	[16, 50]
11	[0, 2, 1, 4, 3]	41	[12, 11, 35, 3, 7]	71	[17, 16, 50]
12	[0, 2, 1]	42	[12, 11, 35]	72	[18, 16, 52, 17]
13	[0, 2, 3, 1]	43	[12, 2, 0, 4, 11, 3, 6]	73	[18, 17, 53]
14	[0, 2, 3, 4, 1]	44	[12, 2, 0, 7, 11, 15, 4, 3]	74	[2, 0, 1, 3]
15	[0, 2, 4, 1, 6, 3, 5]	45	[12, 2, 4, 0, 18, 5, 7, 3]	75	[2, 0, 3, 1, 6, 7]
16	[0, 2, 4, 7, 1, 3]	46	[12, 2, 8, 6, 9, 11]	76	[2, 7, 1, 0, 4, 9, 3]
17	[0, 2, 8, 1, 3]	47	[12, 23, 11]	77	[2, 7, 1, 0, 6, 5, 4]
18	[0, 2, 8, 3, 7, 11, 12, 6, 1]	48	[12, 23, 15, 7, 11]	78	[3, 0, 1, 2, 6, 4]
19	[0, 2, 8, 7, 11, 3, 4, 6, 1]	49	[12, 23, 15, 7, 6, 4]	79	[3, 2, 0, 1]
20	[0, 5, 4, 2, 10, 9, 1, 3]	50	[12, 23, 6, 4]	80	[3, 2, 1, 0, 5, 6]
21	[0, 5, 4, 2, 13, 3, 9]	51	[12, 27, 10, 0, 7, 3]	81	[3, 7, 0, 2, 8]
22	[0, 5, 4, 2, 3, 1]	52	[12, 27, 19, 11]	82	[3, 8, 11, 25, 9]
23	[0, 5, 4, 2, 6, 3, 9, 7]	53	[12, 3, 7, 11, 15, 6, 0, 2, 1]	83	[3, 8, 2, 7, 0, 1, 6, 4, 5]
24	[0, 9, 2, 7, 5, 1, 4, 3]	54	[12, 3, 7, 11, 23]	84	[4, 7, 3, 6, 0, 2, 9, 8]
25	[10, 1, 11, 34, 0, 6]	55	[12, 3, 7, 2, 11, 6, 0, 1]	85	[6, 0, 4, 1, 3, 9, 8, 2]
26	[11, 0, 1, 43, 3, 7]	56	[12, 3, 7, 2, 32, 4]	86	[6, 5, 11, 1, 0, 7, 10, 4, 2]
27	[11, 0, 2, 13, 5, 3]	57	[12, 3, 7, 25, 1, 6, 0, 2, 4]	87	[6, 5, 3, 2, 4, 0, 1]
28	[11, 0, 2, 19, 15, 7, 3, 4]	58	[12, 3, 7, 35, 11]	88	[7, 2, 1, 3, 0, 10, 4]
29	[11, 0, 23, 15, 6, 2, 3, 4]	59	[12, 38, 7, 0, 11]		
30	[11, 0, 23, 15, 7, 6, 4]	60	[12, 39, 7, 6, 4]		

Supplementary 1 A: The NIBs data collected for simulations taken with the second 2D CA Model, associated to Fig 4 A. Shows the list of NIBs for each colour in Fig 4 A. Parameters were ro = 100, co = 100, Period_PM1 = 160, Period_PM2 = 240, t2 = 0, E = 90, R = 26 # neigh = 2, θ = 0.4. The sinus node was in position (10,10) and the ectopic node was in position (26,26)

1	[0, 1]	31	[1, 3, 0, 2, 4]	61	[27, 33, 0]
2	[0, 2, 1, 3, 4]	32	[1, 3, 10, 2, 0, 9, 4]	62	[27, 34]
3	[0, 2, 1, 3]	33	[1, 3, 14, 0, 4, 8, 5, 7, 2]	63	[36, 48]
4	[0, 2, 1, 4, 3]	34	[1, 3, 2, 0, 4, 5]	64	[37, 48]
5	[0, 2, 1]	35	[1, 3, 2, 0, 4, 6]	65	[37, 49]
6	[0, 2, 3, 1]	36	[1, 3, 2, 0, 4]	66	[38, 49]
7	[0, 2, 6, 1, 3, 4]	37	[1, 5, 0, 6, 3, 2, 4]	67	[38, 50]
8	[0, 2, 6, 1, 3]	38	[1, 6, 0, 2, 3, 4, 7]	68	[39, 49]
9	[0, 3, 1, 2]	39	[1, 6, 11, 2, 0, 3, 5, 10]	69	[39, 50]
10	[0, 3, 1, 5, 2, 4]	40	[1, 6, 11, 2, 0, 3, 5, 4]	70	[40, 51]
11	[0, 3, 2, 1, 4, 5]	41	[1, 6, 7, 3, 5, 0, 10]	71	[5, 10, 2, 4, 1, 0, 3, 17]
12	[0, 3, 2, 1, 4, 6]	42	[1, 6, 7, 3, 5, 0, 2, 4]	72	[5, 13, 6, 0, 14, 2, 4, 3]
13	[0, 3, 2, 1, 4]	43	[1, 9, 3, 8, 0, 11, 5, 4]	73	[5, 18, 1, 0, 21, 8, 2]
14	[0, 3, 2, 1]	44	[16, 9, 0, 4, 8]	74	[5, 20, 0, 14, 1, 4, 3, 2]
15	[0, 3, 2, 8, 1, 5]	45	[24, 1, 0, 21, 8, 2]	75	[5, 20, 0, 21, 9, 2]
16	[0, 4, 1, 3, 2]	46	[24, 1, 0, 3, 17, 9]	76	[5, 3, 0, 2, 4, 1, 13]
17	[0, 4, 2, 3, 1, 6]	47	[24, 1, 0, 4, 3, 23, 2]	77	[5, 3, 1, 0, 2]
18	[0, 5, 1, 2]	48	[26, 0, 2, 28]	78	[5, 3, 2, 0, 4, 1, 8]
19	[0, 5, 1, 8, 2, 6, 3]	49	[26, 0, 22, 9, 3]	79	[5, 3, 4, 1, 0, 17, 2]
20	[0, 6, 1, 7, 3, 2, 5]	50	[26, 0, 22, 9]	80	[5, 3, 4, 1, 0, 2, 7]
21	[0, 6, 3, 1, 2, 4, 5, 7]	51	[26, 0, 27, 4]	81	[5, 3, 8, 1, 0, 17, 2]
22	[0, 6, 3, 1, 2, 4]	52	[26, 0, 3, 28, 4]	82	[5, 9, 3, 4, 1, 0, 10, 8, 2]
23	[0, 6, 3, 5, 4, 1]	53	[26, 0, 3, 28]	83	[7, 16, 1, 0, 4, 8, 3, 9]
24	[1, 14, 3, 5, 0, 10, 4]	54	[26, 0, 32, 4]	84	[8, 0, 1, 3, 2]
25	[1, 14, 3, 5, 0, 12, 10]	55	[26, 0, 32]	85	[9, 16, 0, 2, 18, 10]
26	[1, 2, 0, 3, 6, 10]	56	[26, 0, 33]	86	[9, 16, 0, 4, 27]
27	[1, 24, 0, 4, 16, 10]	57	[26, 0, 34]	87	[9, 6, 0, 11, 4, 3, 2]
28	[1, 24, 0, 4, 5, 10, 7]	58	[26, 0, 4, 16, 10]		
29	[1, 24, 0, 4, 6, 2, 17]	59	[26, 0, 4, 27]		
30	[1, 24, 0, 8, 2, 6, 9, 3]	60	[26, 0, 6, 8, 16, 7]		

Supplementary 1 B: The NIBs data collected for simulations taken with the second 2D CA Model, associated to Fig 4 B. Shows the list of NIBs for each colour in Fig 4 B. Parameters were ro = 100, co = 100, Period_PM1 = 160, Period_PM2 = 240, t2 = 0, E = 90, R = 26 # neigh = 2, θ = 0.4. The sinus node was in position (10,10) and the ectopic node was in position (51,51)

1	[0, 1, 2]
2	[0, 1]
3	[0, 2, 1]
4	[0, 2, 3]
5	[0, 2]
6	[0, 3, 1, 4]
7	[0, 3, 1]
8	[0, 3, 2]
9	[0, 3, 4, 1]
10	[0, 3, 4]
11	[0, 3]
12	[0, 4, 1, 3]
13	[0, 4, 1]
14	[0, 4, 3, 1]
15	[0, 4, 3]
16	[0]
17	[1, 4, 5]
18	[1, 4]
19	[1, 5, 2]
20	[1, 5, 4]
21	[1, 5, 6, 2]
22	[1, 5]

Supplementary 1 C: The NIBs data collected for simulations taken with the second 2D CA Model, associated to Fig 4 C. Shows the list of NIBs for each colour in Fig 4 C. Parameters were ro = 100, co = 100, Period_PM1 = 160, Period_PM2 = 240, t2 = 0, E = 90, R = 26 # neigh = 2, θ = 0.4. The sinus node was in position (10,10) and the ectopic node was in position (76,76)

Aortic Valve Replacement via Mini-Sternotomy: Results of a Single Centre Analysis

JOE HARRINGTON, SEÁN BARRETT, EILEEN DUGGAN, KISHORE DODDAKULA

Abstract

BACKGROUND: The traditional method of Aortic Valve Replacement (AVR) is via full sternotomy. However, this incision may not heal properly and cause significant pain. Minimally invasive approaches have been adopted, including mini sternotomy. These have gained popularity due to smaller incision, reducing surgical trauma. The hypothesis is that AVR via mini sternotomy is a safe alternative to full sternotomy. The objective was to analyse and describe results of patients who underwent the procedure, including post-operative outcomes.

METHODS: A retrospective database review was performed on patients who underwent AVR via mini-sternotomy between September 2016 and December 2022 in Cork University Hospital (CUH). Exclusion criteria included patients who had an aortic procedure concurrently, such as ascending aorta replacement, and those under 18 years. Results for variables, such as age, were expressed as a mean.

RESULTS: 93 patients were included; the average age was 68. Average bypass and cross-clamp times were 92 and 73 minutes respectively. Median post-operative length of stay was 8 days and median ICU length of stay was 3 days. There were no in-hospital mortalities.

CONCLUSION: This study was completed through a retrospective chart and database review of patients who underwent AVR via mini sternotomy over a 6-year period. The results presented provide valuable information related to patient demographics and peri- and post-operative outcomes. This is the first such chart study related to this procedure in an Irish hospital context.

Introduction

Aortic valve disease is the most common valvular heart disease affecting millions of people worldwide and the aortic valve is the most commonly replaced heart valve [1]. Aortic valve replacement is the standard treatment for patients with severe or symptomatic aortic stenosis or aortic regurgitation/insufficiency [2]. It was first performed by Harken and Starr in 1960 at the Peter Bent Brigham Hospital in Boston through a full median sternotomy incision [3]. The traditional method of aortic valve replacement is via full sternotomy where an incision is made from the top of the sternum down as far as the umbilicus potentially. However, this long midline incision may not heal properly, may cause a significant amount of pain and may be associated with a prolonged recovery [2]. In patients with conditions such as osteoporosis or diabetes, the thinned out sternum may take a longer than expected time to heal and may lead to severe pain for patients [2]. AVR via mini-sternotomy has cosmetic advantages and is particularly useful in frail patients who may suffer from a conventional sternotomy and associated morbidities [3]. Worldwide, the number of aortic valve replacements in 2003 was 290,000 and is predicted to be 850,000 by 2050 [4].

Over the last two decades, a minimally invasive approach to aortic valve replacement has been adopted by many surgeons internationally [5]. It has generally been accepted as an alternative to a full sternotomy approach in low-risk patients, but there is limited data for its use in high-risk patients. The technique was first described by Cosgrove and Sabik in 1996, but the surgical uptake since then has been patchy [6]. This has been due possibly to the need for extra training for surgeons and the belief that there

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is no surgical benefit compared to the full sternotomy approach. However, the use of the approach has increased in frequency in Europe in recent years [7].

This paper presents a retrospective review of one such minimally invasive technique, the mini sternotomy approach, in Cork University Hospital (CUH). This procedure has been performed by Mr. Kishore Doddakula and his colleagues since 2011. This retrospective database review aims to explore the characteristics of patients who have undergone a minimally invasive aortic valve replacement and examine the outcomes for identified patients.

Materials and Methods

This study was conducted in the Department of Cardiothoracic Surgery, CUH. A retrospective review was performed on a prospectively collected database of patients who underwent aortic valve replacement (AVR) via mini sternotomy between September 2016 and December 2022 (inclusive). Data was gathered from the PATS (Patient Advocate Tracking System) database in the Department of Cardiothoracic Surgery and was then entered into a data collection sheet, which consisted of parameters such as bypass time, cross-clamp time, and length of post-operative stay. Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC).

Patients aged 18 years or older who underwent an AVR via mini sternotomy were included in the study. Patients younger than 18 years old, those who underwent a full sternotomy and those who had another cardiac procedure at the same time (such as aortic root replacement or coronary artery bypass graft) were excluded.

Data analysis was performed using Microsoft Excel. Basic descriptive analysis was used to characterise the data. Results for continuous numerical variables such as age, height and weight were expressed as means. Categorical variables such as sex and comorbidities were expressed as percentages.

Results

A total of 93 patients were included in the study, after the exclusion criteria were applied. Tables 1 to 3 present a summary of the results of the study and data analysis. Table 1 presents the demographic data as the demographic parameter and the corresponding parameter number (n), Table 2 summarises the peri-operative outcomes with the time presented as the average time and also as a range. Table 3 summarises the post-operative outcomes and complications.

The patient demographic data shows that the procedure was performed on more male than female

Table 1: Demographic Data

Demographic Parameter	Parameter Number (n)
Age (years)	68
Number of males	52 (55.9%)
Number of females	41 (44.1%)
Height (m)	1.67
Weight (kg)	81
BMI (kg/m^2)	29
Diabetes	10 (10.8%)
Hypertension	61 (65.6%)
Hyperlipidaemia	68 (73.1%)
Coronary Artery Disease	13 (14%)
Pre-Existing Arrhythmia	18 (19.4%)
Smoker/Ex-Smoker	48 (51.6%)
COPD	17 (18.3%)
Cardiac Ejection Fraction (%)	54
Creatinine Clearance (ml/min)	84

Table 2: Peri-Operative Outcomes

Peri-Operative Outcome Parameter	Average Time (Range)
Operative time (mins)	243 (140-465)
Cardio-pulmonary bypass time (mins)	93 (56-138)
Cross-clamp time (mins)	72 (39-105)
Ventilation time (hours)	16 (1-90)
Length of ICU stay (days)	3 (1-65)
Length of hospital stay (days)	11.1 (5-85)

Table 3: Post-Operative Outcomes and Complications

Post-Operative Outcome Parameter	Number of Procedures
Conversion to Full Sternotomy	3
Re-do Sternotomy	5
Sternal Wound Infection	2
Myocardial Infarction	0
Paravalvular Leak	1
Stroke	1
Acute Kidney Injury	0
Arrhythmias	25
Pulmonary Embolism	0
Deep Vein Thrombosis	0
Prolonged Use of Inotropes	18

patients. The most common pre-operative patient conditions were hypertension and hyperlipidaemia, both for over 65% of patients. Pre-existing arrhythmia was evident for approximately 20% of patients and approximately 50% of the patients had a history of smoking.

The mean operative time was approximately 4 hours, with average ICU and hospital stays of 3 and 11 days respectively yielding a mean post-operative length of stay of 8 days. Mean bypass and cross-clamp times were 92 and 73 minutes respectively.

A range of post-operative outcomes are presented. Arrythmias were found in 25 patients (26.9%) in comparison to 19.4% of patients identified with the condition pre-operation. Conversion to a full sternotomy was undertaken for only 3 patients (3.2%) and a re-do sternotomy was performed on 5 patients (5.4%). 18 procedures (19.3%) involved the use of inotropes. There were no in-hospital myocardial infarctions, pulmonary embolisms, deep vein thromboses or in-hospital mortalities.

Figures 1 and 2 present two examples where the full dataset is presented without filtering as a scatter diagram. Both figures show clustered data with two outlier points where long periods of hospitalisation were required. A Pearson correlation analysis indicates a stronger correlation with the removal of these two outliers, although the correlation value remains relatively low at 0.25 for the relationship in Figure 1 and very low at 0.1 for the relationship in Figure 2.

Discussion

Minimally invasive aortic valve replacement has gained increasing popularity over the last 20 years by avoiding a full sternotomy incision, subsequently reducing surgical trauma [8]. Any kind of minimally invasive cardiac surgery is technically more challenging than a procedure performed through a full median sternotomy, mainly due to a limited incision and

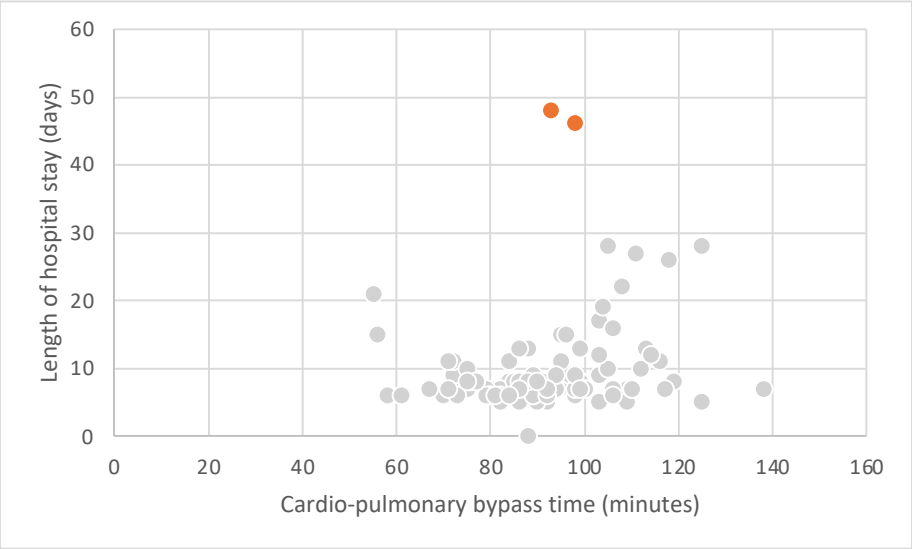

Figure 1 Cardio-Pulmonary Bypass Time versus Length of Hospital Stay

a smaller operative space that leads to restricted manoeuvrability [9]. A steep learning curve associated with minimally invasive aortic valve replacement has been found in several studies, even those involving the most experienced and skilled surgeons [10]. The limited view of the operative field obstructs access to the ascending aorta and may prevent desired sight of the procedure, potentially leading to longer operative times [11]. Despite the complexity of the procedure, it has been shown that there is no increase in early mortality when compared with a conventional aortic valve replacement [6].

This approach has been shown to reduce postoperative morbidity, provide a faster recovery and rehabilitation time, a shorter hospital stay and better cosmetic results compared with conventional surgery [5]. However, the procedure is more technically demanding and difficult for surgeons, which increases the likelihood of errors, especially in those with limited experience. A J-shaped mini sternotomy is the most commonly employed minimally invasive approach [12]. This is performed by making a 2-3 inch incision along the upper part of the sternum. In addition to providing improved cosmetic results compared to a full sternotomy, the smaller incision reduces the likelihood of the development of wound infections, especially in those who are obese or have diabetes [13].

This paper presents valuable results based on a retrospective database review on patients who underwent AVR via mini sternotomy between September 2016 and December 2022 at CUH. Results are presented for the patient demographics, peri-operative outcomes and complications with key results identified.

The key results of the study are as follows:

- For the patient group a large number and a wide variety of co-morbidities were found with the most common being hypertension and hyperlipidaemia at 65% and 73%, respectively.
- For the peri-operative outcome parameters the average value and the range are presented with the range in particular for the ventilation time, length of ICU and length of hospital stay being broad.
- For the post-operative outcome parameters a notable finding was that there was an increase in the incidence of arrhythmias from 18 to 25 for the patient cohort studied. In addition, there were no in-hospital myocardial infarctions, pulmonary embolisms, deep vein thromboses or in-hospital mortalities.

Conclusions

The objective of the study presented in this paper was to analyse and describe results of patients who underwent aortic valve replacement via mini sternotomy including post-operative outcomes. This was completed through a retrospective chart and database review of patients who underwent this procedure between September 2016 and December 2022 in CUH. Data for 93 patients (after the application of exclusion criteria) was analysed through Excel. The results are presented and described, providing valuable information related to patient demographics and peri- and post-operative

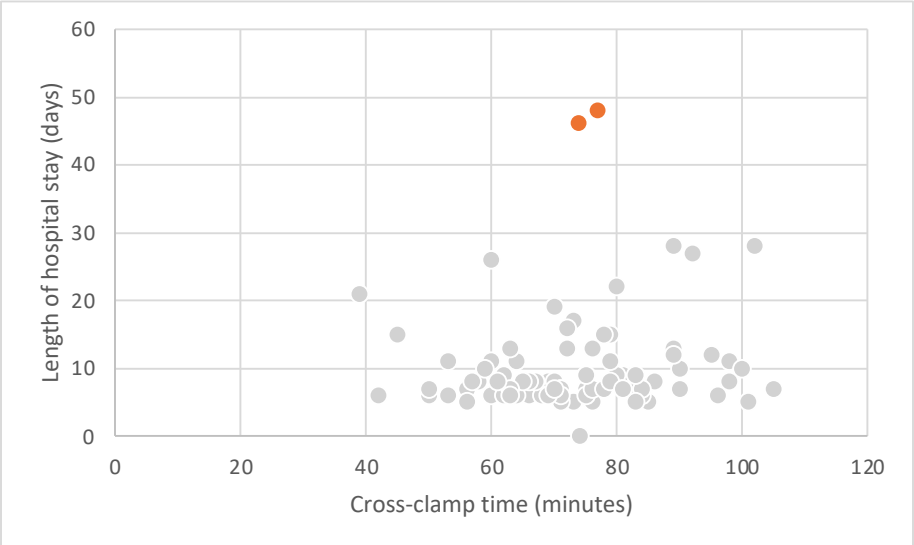

Figure 2 Cross-Clamp Time versus Length of Hospital Stay

outcomes.

It is the first such study related to AVR via mini sternotomy in an Irish hospital context and increases the national knowledge database for this minimally invasive surgical technique.

Acknowledgments

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Cancer Cachexia and Dysphagia: A Systematic Literature Review

MARK LEAHY

Abstract

BACKGROUND: Dysphagia is a difficulty in swallowing. Cancer cachexia is a generalised muscle loss disorder common in patients with late-stage disease. The prevalence of dysphagia in patients with head and neck cancer is well documented. However, it is postulated that cancer cachexia can, through systemic muscle loss, cause weakening of swallowing muscles and dysphagia. This review aimed to evaluate the scope of the association between cancer cachexia (excluding head and neck cancer) and dysphagia.

METHODS: A systematic review was conducted using the PRISMA P guidelines. PubMed and Embase databases were searched for papers including terms related to (1) cancer, (2) cachexia and (3) dysphagia. Results were imported to Zotero software manager, where duplicates were removed. The remaining articles were screened using pre-determined eligibility criteria. Eligible papers were retained for data extraction, data synthesis and narrative synthesis. Risk of bias was evaluated using the CASP cohort and case control tools.

RESULTS: Four studies met the eligibility criteria. These papers reported an association between cancer cachexia and dysphagia, with odds ratios of 2.1 [P=0.033] and 1.8 [P=0.018]. Prevalence of dysphagia was 16% higher in cancer patients with cachexia.

CONCLUSION: These findings suggest a positive association between cancer cachexia and dysphagia. However, due to the limited number of papers included, their heterogeneity and their limitations, it is difficult to draw a robust conclusion. Sarcopenia or neurodegenerative disease may have contributed to these results. Regardless, these four studies support the requirement for dysphagia assessment in patients with cancers outside swallow regions.

Background

Dysphagia, defined by the Royal College of Speech and Language Therapists (RCLST), pertains to eating and drinking disorders that can affect the oral, pharyngeal, and oesophageal stages of deglutition [1]. It involves the intricate interplay of respiratory, oral, pharyngeal, laryngeal, and oesophageal structures working in harmony to propel a bolus to the stomach. Muscular and sensory innervation of these structures is vital. Swallowing impairment is often due to structural changes, inflammation at any point along the bolus pathway, neurological issues, or muscular deficits. Diagnosis involves a combination of assessments, including a detailed case history, cranial nerve evaluation through an oral-motor examination, bedside food and fluids trials, and objective swallowing assessments such as videofluoroscopic swallowing studies (VFSS), fibre-optic endoscopic evaluation of swallowing (FEES), and high-resolution pharyngeal manometry [2].

Dysphagia can occur in the oropharyngeal and oesophageal stages. Oropharyngeal dysphagia results from dysfunction in structures like the lips, teeth, tongue, epiglottis, hard and soft palates. It is often associated with head and neck cancers and their radiotherapy [3]. Esophageal dysphagia, on the other hand, relates to the inability to propel the bolus from the oropharynx to the stomach. It may be caused by obstructions (e.g., stricture or tumour) or functional (mechanical) disorders like nerve damage, esophagitis, or achalasia.

Dysphagia is a common complication in cancer patients [4] and a complex condition influenced by several cancer-associated factors. Head and neck

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tumours have a direct impact on swallowing, with dysphagia present in 89% of patients with head and neck cancer [5]. It can be attributed to tissue loss, structural damage, or obstruction due to the tumour mass. Tumours in the brain or brainstem can disrupt neural connections, affecting swallowing [6]. Aspiration pneumonia is a frequent consequence of dysphagia [7] and contributes to the mortality of head and neck cancer patients [8]. The association between head and neck cancer and dysphagia is well-documented, but dysphagia in cancers outside the swallowing regions is underexplored [5].

Cancer treatment, including tumour resection, radiotherapy, and chemotherapy, can impact dysphagia. Head and neck surgery may leave tissue scarring, reducing muscle function and potentially impairing swallowing coordination if nerves are damaged. Radiotherapy's impact on dysphagia depends on the irradiation site. It damages DNA in rapidly proliferating cells, leading to tumour cell destruction but may also harm healthy tissue organelles, causing transient cell damage and leading to acute dysphagia. Additionally, radiation may induce chronic dysphagia through tissue fibrosis, reducing muscle function and causing atrophy [9]. This study focuses on the aspect of dysphagia related to muscle mass loss.

Cachexia is a complex weight loss disorder caused by illness. The condition is characterised by severe and unintentional loss of muscle (and fat mass in some cases) which cannot be fully reversed by nutrition. Cachexia affects 50-80% of cancer patients [10], particularly in late-stage cancer. Cancer cachexia requires a meticulous multimodal clinical examination for diagnosis. The condition is defined as “weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion” [11].

Muscle wasting in cancer cachexia primarily involves inflammation. Tumours boost the production of inflammatory mediators and tumour-derived compounds, like proteolysis-inducing factor (PIF), which breaks down myofibrillar proteins. PIF and cytokines activate nuclear factor-kB, leading to skeletal muscle atrophy, as well as janus kinase MAPK cascades, resulting in apoptosis and cell death [12].

Cachexia affects metabolic pathways as tumours demand significant glucose and amino acids for their proliferation. Skeletal muscle proteins are often broken down to produce glutamine for tumour protein synthesis and alanine for glucose production in the liver. To maintain homeostasis in the presence of a tumour, substantial metabolic changes occur, causing systemic skeletal muscle loss [13]. This cachectic muscle loss is not confined to the tumour's immediate vicinity, reflecting the systemic characteristic of cancer-mediated inflammation.

Cancer cachexia is associated with poor prognosis [14]. Patients achieve low scores in quality-of-life surveys and the Karnofsky Performance Scale, and regularly present with decreased food intake, fatigue and reduced range of motion [15]. Cancer cachexia accounts for 20% of cancer deaths, which typically ensues as weight loss surpasses 30-40% [16]. There is a clear association between cachectic muscle loss and reduced food intake. There is also an association between generalised muscle loss and dysphagia. However, systemic muscle loss due to cachexia is not well investigated as a factor which contributes to dysphagia.

Dysphagia in patients with unrelated cancer is frequently overlooked, which could result in poorer patient quality of life, impaired nutrition or aspiration pneumonia in later-stage patients. Dysphagia could, through a cachectic muscle loss mechanism, arise in patients with cancers unrelated to swallow function [17] . However, few studies have identified cachexia as a causal factor for dysphagia. This systematic review of the literature aims to evaluate the scope of the association between cancer cachexia (excluding head and neck cancer) and dysphagia.

Methods

SOURCE

The databases used for this review were PubMed and Embase. These were selected for their advanced searching functions and facilitation of the use of Medical Subject Heading (MeSH) terms. PubMed was chosen over MEDLINE as PubMed contains additional content outside the scope of the MEDLINE database. Additional related papers were also assessed through referencing lists (PubMed’s “Related citations” feature and Embase’s “Find Similar” features); however none were deemed eligible for this review. Database searching was the only source of data included in this review.

SEARCH STRATEGY

Preliminary searches were performed in January 2022, however minor adjustments were made to the search terms. The terms "tumour" and "tumours" were added to increase the number of papers identified. The final search was performed on 25 February 2022. Identical terms were used in each database. Neither search utilized a timeframe. The search terms used for PubMed were (cancer[Title] OR cancers[Title] OR tumour[Title] OR tumours[Title] OR tumour[Title] OR tumours[Title] OR malignancy[Title] OR malignancies[Title] OR carcinoma[Title] OR carcinomas[Title]) AND (cachexia OR sarcopenia OR malnutrition OR atrophy OR "muscle wastage" OR "muscle wasting") AND (dysphagia OR 'eating-related stress' OR 'difficulty swallowing' OR "trouble swallowing" OR "swallowing disorder" OR "swallowing disorders" OR "deglutition disorder").

"Cancer" and related terminology referred to the patient population of interest. The MESH terms related to cancer were specified to have been included in the title to ensure that populations were cancer-specific and not related to another disease. The Embase search included ":ti" after each cancer-related term, to ensure that those terms must be included in the title, mirroring the PubMed search. No other restrictions were used to maximise the scope of the search.

The exposure was "cachexia" and other muscle loss-related terms. This search encompassed anorexia cachexia syndrome. "Sarcopenia" was added to include papers which may have grouped together these nutrition-based disorders, as seen during early database searches.

The outcome was searched using "dysphagia" and a few other terms related to deficits in swallowing. Prior to protocol completion, preliminary searches identified "difficulty swallowing" and other such terms as being used interchangeably. While the absence of the term "dysphagia" may be indicative of the use of a weak definition, "swallowing" terminology was included to capture a wider array of papers.

INCLUSION CRITERIA

Studies included in the review were required to include full free-text links and to have been written in English. All years were included. Only observational studies were assessed, including cohort, case-control, cross-sectional and case series studies. Patient demographics must have been over the age of 18. Patients with primary tumours outside the head, neck, and upper gastrointestinal tract were included. Papers which included these cancers but accounted for primary cancer site as a covariate in the statistical analysis were also included.

EXCLUSION CRITERIA

Interventional studies, such as randomised controlled trials, were all excluded. This review focused purely on the association between cancer cachexia and dysphagia. Therefore, studies focusing on treatment efficacy would not provide useful results. Research papers without free access or access through Embase or PubMed subscription were excluded. The review was patient-focused, excluding animal and preclinical models.

Regarding cancer types, a number were excluded due to their potential to impact dysphagia through a non-cachectic mechanism. Papers with a sole focus on cancers of the head and neck, and upper gastrointestinal tract were excluded, as these are seen to impact dysphagia directly. Gastric cancers have been linked to dysphagia and were also excluded (Maconi et al., 2008). The review also excluded patients with neurodegenerative diseases. Patients who had undergone radiotherapy or surgery interventions to the chest, head or neck regions were also excluded.

STUDY SELECTION

Results of the database searches were imported to Zotero Software Manager. This program facilitated the storage of citations and was also used to merge duplicate papers. Merging was performed manually with the most recent version of a text retained. The data of the remaining citations were imported into Microsoft Excel for the initial screening. Texts were evaluated based on title and abstract and were removed based on inclusion and exclusion criteria. Remaining papers were sought for retrieval. Those with accessible free full-text articles were thoroughly evaluated for eligibility criteria. Four papers fit these criteria and were retained for the final review. The Prisma 2009 Flow Diagram was used to record the number of papers at each stage of the screening process.

DATA EXTRACTION

Data were extracted using a specialised data

extraction form in line with the PICO framework that was designed to fit the research (see Appendix 1). Information was extracted under seven headings. Bibliographical information included the title, author, and funding source. The objectives column captured the aims of each paper. The study design and methodology column included data on study type, population type, recruitment methods, sample size, eligibility criteria and a brief overview of the study. In the exposure column, patient characteristics and cachexia definition were recorded. Outcomes included the definition of dysphagia. The results column recorded the association between cancer cachexia and dysphagia noted in each paper, as well as any relevant notes or conclusions in the paper relevant to these associations. A strengths and limitations column was also added to assist in gathering data that would help evaluate these papers.

QUALITY ASSESSMENT

Risk of bias and overall study quality was evaluated using the CASP Cohort and Case-Control checklists. Of the four selected papers, two were cross-sectional studies, one was a case-control study, and one was a post hoc analysis of prospective cohort data. CASP tools were chosen over other tools as use of the same type of tool facilitated a more thorough comparison. The use of the cohort tool for cross-sectional studies meant that questions 6. (a) and 6. (b), relating to follow-up (Table 4) were non-applicable and were excluded. Using the Web of Science database, the number of citations of each paper was recorded.

SYNTHESIS OF RESULTS

A narrative approach was taken to data synthesis. Different statistical approaches were taken by each paper, and the use of meta-analysis with both odds ratios and prevalence values may have generated unreliable results. There was significant heterogeneity between exposure measurements and outcome definitions used in each paper and therefore a comparison between their findings was made in the context of these definitions and not in a quantitative manner. Relevant findings of the four selected papers were synthesized in three tables, examining study characteristics, participant characteristics and results.

Results

SEARCH RESULTS

712 papers were screened by title and abstract, resulting in the retrieval and evaluation of 59 texts based on eligibility criteria. Four studies met these criteria and underwent quality appraisal and data extraction. The PRISMA diagram (Fig. 1) displayed exclusion criteria for eliminating full-text articles. Results of each paper were synthesized in Table 1, 2, and 3.

DESCRIPTION OF STUDIES

Out of the four selected studies, two were cross-sectional [18,19], one was a case-control [20], and one was a post hoc analysis of prospective cohort data [21]. These studies were conducted in developed countries, with two in Japan [19,20], one in Ireland [18], and one in the US [21]. Their objectives varied, with two studies aimed at identifying factors contributing to eating-related distress and dysphagia [18,19], one focused on generating a symptom profile for cancer anorexia cachexia syndrome [21], and one examined the association between skeletal muscle and dysphagia [20]. Kenny et al., 2019, and Lasheen and Walsh., 2010 had relatively large sample sizes of 385 and 484, respectively. Amano et al., 2018, and Wakabayashi et al., 2015 had comparatively smaller sample sizes of 140 and 111, respectively, while still generating similar p-values when compared to the larger studies.

DEMOGRAPHIC CHARACTERISTICS

Differences among participants in each paper included variations in mean patient age: 66, 66, 65, and 70 [18,19,21,20]. The primary tumour site differed, with lung being most common in Amano et al., 2018 (22.1%) and Lasheen and Walsh., 2010 (23%), while Kenny et al., 2019 (15.3%) and Wakabayashi et al., 2015 (11.7%) had lung tumours as the second most common. Colorectal (21.3%) and oesophageal (49.5%) cancer predominated in these papers. Kenny et al., 2019 was the sole study excluding head and neck cancers.

Two studies had all participants with metastatic cancer [19,21]. Kenny et al., 2019 (67%) and Wakabayashi et al., 2015 (26%) displayed significant differences in the proportion of participants at the metastatic stage.

Regarding treatment, limited data was available in Lasheen and Walsh., 2010, stating that "few patients were receiving active treatment." In Kenny et al., 2019, all patients were under treatment, mainly chemotherapy (74%). Amano et al., 2018 saw 63.6% of patients receiving chemotherapy. Information on

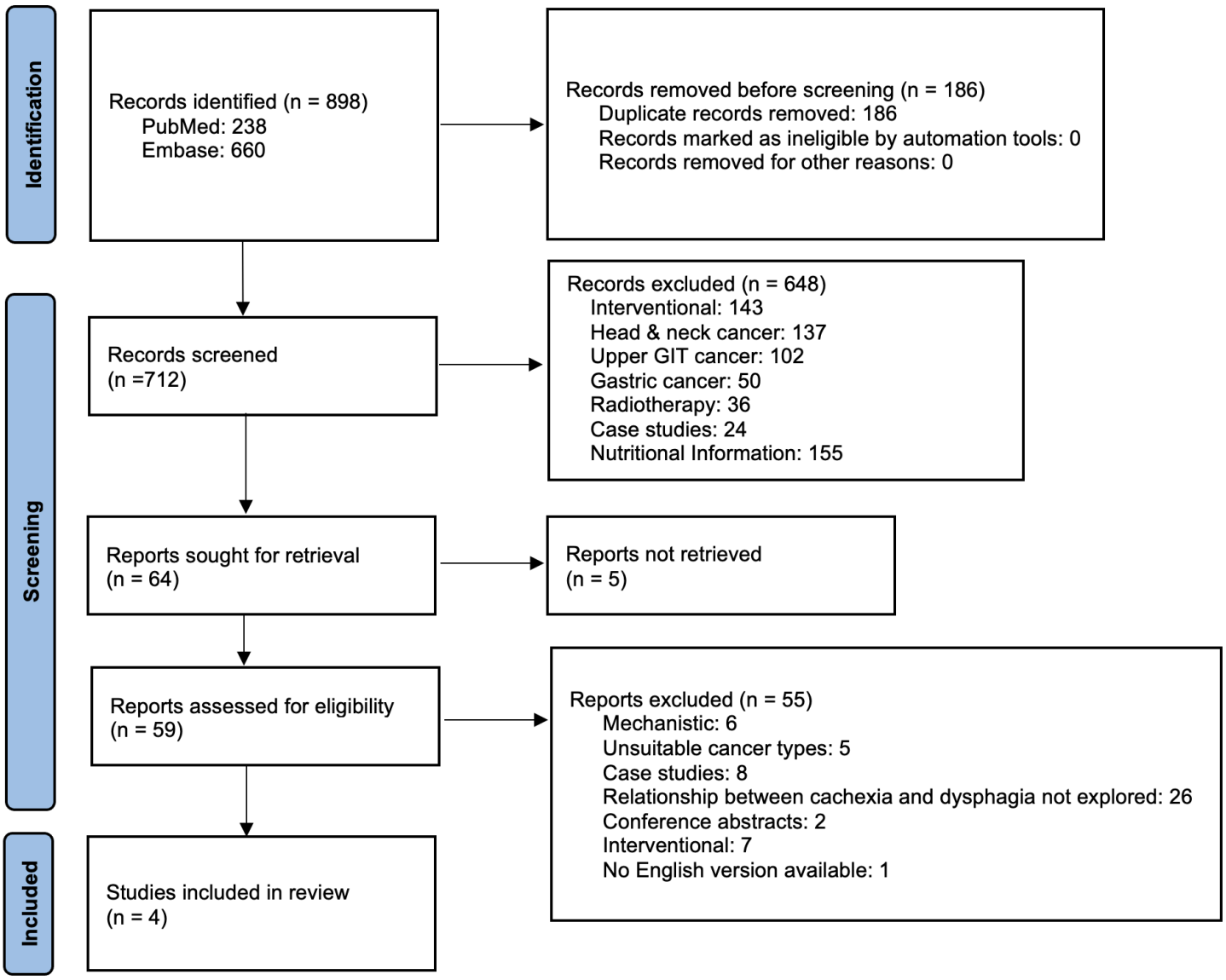

Figure 1: Prisma Diagram

the number of patients receiving radiotherapy was not provided in three studies [19,21,20], and one study reported patients who had undergone surgery [20].

EXPOSURE CHARACTERISTICS

Differences were observed in cachexia measurements and definitions among these papers. Three papers [18,19,21] relied partially on self-reported height and weight data, with two of them [18,21] supplementing this with validated medical records. In contrast, the fourth study [20] used abdominal CT scans to assess skeletal muscle mass instead of BMI. While two papers [18,19] adhered to the international consensus diagnostic criteria for cachexia, which include a 5% body weight loss in 6 months or a BMI under 20 kg/m^2 with a 2% weight loss in 6 months, Lasheen and Walsh., 2010 defined cachexia as a loss exceeding 10% of pre-illness body weight. Wakabayashi et al., 2015 did not employ a validated cachexia definition and measured skeletal muscle index using the psoas muscle area divided by height squared.

OUTCOME CHARACTERISTICS

Variability was evident in the measurement tools and definitions of dysphagia. Three studies [18,19,21] employed patient questionnaires, with one adding a cranial nerve examination [18]. The fourth study20 utilized a 10-point observer-rating scale. Of these, two measurement tools were validated [18,20], while two were unvalidated [19,21].

RESULTS

Despite methodological heterogeneity among these papers, the association between cachexia and

Table 1: Study Characteristics

Author & Year	Title	Country	Sample Size	Population & Setting	Study Design	Aims & Objectives
(Kenny et al., 2019)	Dysphagia Prevalence and Predictors in Cancers Outside the Head, Neck, and Upper Gastrointestinal Tract	Ireland	N=385	Patients with cancer outside the head, neck, or upper GI tract attending two acute hospitals and one hospice.	Cross-sectional	[1] To address gaps in dysphagia identification and management. [2] To profile those most at risk of swallowing difficulties by examining clinical and demographic factors that may influence dysphagia presence.
(Amano et al., 2018)	Eating-related distress in advanced cancer patients with cachexia and family members: a survey in palliative and supportive care settings	Japan	N=140	Palliative care patients in Osaka City General Hospital (all advanced cancer patients).	Cross-sectional	[1] To examine the severity of nutrition impact symptoms in advanced cancer patients and the prevalence of eating-related distress among patients and their family members in palliative and supportive care settings, including outpatient services, palliative and supportive care teams, and the palliative care unit. [2] To compare these parameters between the following groups: (1) non-cachexia/pre-cachexia and (2) cachexia/refractory cachexia.
(Lasheen and Walsh., 2010)	The cancer anorexia-cachexia syndrome: myth or reality?	USA	N=484	One thousand consecutive cancer in- and out-patient consults to the palliative medicine team.	Post hoc analysis of prospective cohort data	[1] To identify the clinical symptom characteristics of CACS. [2] To evaluate CACS independent impact on patient outcomes, assessed by symptom burden, and survival from the time of referral.
(Wakabayashi et al., 2015)	Skeletal muscle mass is associated with severe dysphagia in cancer patients	Japan	N=111	Cancer patients with dysphagia admitted to the Yokohama City University Medical Center and referred to the department of rehabilitation medicine between May 2010 and April 2014.	Case-control	[1] To investigate the association between skeletal muscle mass assessed by abdominal CT, ADLs and severe dysphagia in cancer patients.

Table 2: Demographic Characteristics

Author & Year	Mean Age (Years)	Primary Cancer Site, (%)	Disease Extent, n (%)	Treatment Status, n (%)
(Kenny et al., 2019)	66 (±12)	Bladder (10.1), Brain (0.2), Breast (7.0), Cervix (0.2), Cholangiocarcinoma (0.8), Colorectal (21.3), Gallbladder (0.1), Kidney (10.9), Liver (1.0), Lung (15.3), Mediastinum (0.2), Melanoma (2.1), Mesothelioma (0.8), Ovary (5.2), Pancreas (5.7), Peritoneal: (0.2), Prostate (13.8), Sarcoma (0.1), Testicle (1.3), Thymus (0.2), Uterus (1.3)	Metastatic 257 (67) Locoregional 128 (33)	Medical oncology 286 (74) Palliative care 91 (24) Radiation oncology 8 (2)
(Amano et al., 2018)	66.3 (±11.1)	Lungs (22.1), Upper and lower gastrointestinal tract (22.1), Liver, biliary system, pancreas (12.9), Haematological malignancy (11.4), Urinary system, prostate (10.0), Head and neck (6.4), Breast (5.7), Gynaecology (3.6), Others (5.7)	Metastatic 140 (100)	Pre-chemotherapy 8 (5.7) Chemotherapy 89 (63.6) Never treated/previous treatment 43 (30.7)
(Lasheen and Walsh., 2010)	65 (21-94)	Lung (23), Colorectal (10), Breast (10), Prostate (18), Pelvic (7)	Metastatic 484 (100)	"Few patients were receiving active treatment"
(Wakabayashi et al., 2015)	70 (±10)	Oesophageal (49.5), Lung (11.7), Gastric (9.9), Brain (5.4), Colon (4.5), Prostate (4.5), Hepatocellular (1.8), Thyroid (1.8), Pharyngeal (1.8), Others (9.0)	Stage I 20 (19) Stage II 19 (18) Stage III 39 (37) Stage IV 27 (26)	Surgery 71 (64) Without surgery 40 (36)

dysphagia remained relatively consistent. While Kenny et al., 2019 and Wakabayashi et al., 2015 examined different factors (cachexia versus skeletal muscle index) and outcomes (dysphagia versus oral food intake), both studies indicated a significant link between muscle loss and swallowing difficulties (2.1 (1.1-4.0) and 1.8 (1.1-3.0), respectively). Cachectic patients had a dysphagia prevalence of 28%, compared to 12% in non-weight loss patients [21]. Amano et al., 2018 also demonstrated increased dysphagia prevalence in cachexia-affected patients (2(0-5)) compared to non-cachectic patients (0(0-2)). All four papers reported similar p-values, indicating statistical significance: $P=0.033$ [18], $P=0.002$ [19], $P<0.05$ [21], and $P=0.018$ [20].

Regarding control of covariates, three studies considered primary cancer site, one excluding relevant tumours in the study design18, while the others employed logistic regression20,21. Age, gender, and Eastern Cooperative Oncology Group (ECOG) were the common covariates in three of the studies [18,20,21], though Amano et al., 2018 did not adjust for any covariates.

QUALITY OF STUDIES

CASP checklists were employed to assess the quality of these papers, revealing a range of risk or bias, from low to moderate. Three studies were classified as having low bias risk, as they diligently identified and addressed confounding factors to prevent them from impacting the results [18,20,21]. However, Amano et al., 2018 failed to identify head and neck cancer as a potential confounder and did not use statistical methods to account for other influencing factors, which raises concerns about the validity of their results, leading to a moderate risk of bias.

Two studies relied on self-reported height and weight data, introducing a slight chance of bias [18,19]. Additionally, two papers used diagnostic tools not specific to dysphagia, and the validity of these tools remains uncertain [19,21]. Only Kenny et al., 2019 provided precise results, indicated by narrow confidence intervals and low p-values. The precision of the other three studies was unclear due to wide confidence intervals [19], unreported confidence intervals [21], and $P<0.05$ reported in only a small number of variables [20].

Three of the studies are applicable to a local population, as they employed validated international definitions and measurement methods that are feasible for replication [18,19,20]. In contrast, Lasheen and Walsh., 2010 provided limited information regarding their dysphagia diagnosis tool, making it unclear whether it's validated or accessible to other populations.

Discussion

This systematic review explored the link between cancer cachexia (excluding head and neck cancer) and dysphagia. The review revealed a higher dysphagia prevalence in cachexic patients, with a consistent, statistically supported association. However, the limited number of included studies and their divergent methodologies, coupled with a moderate bias risk in one study, challenge the ability to establish a definitive conclusion regarding the relationship between cancer cachexia and dysphagia.

The link between skeletal muscle loss and dysphagia is evident in all these papers. Two studies address the relationship between overall muscle loss and dysphagia [18,20], while the other two studies briefly mention the associations. The exact cause of dysphagia in patients with non-head and neck cancer sites remains uncertain [18]. Reduced food intake is a component of cancer anorexia cachexia syndrome [21], and it's reasonable to assume that this reduced intake might be linked to dysphagia. This dysphagia could be influenced by the cachexia aspect of the syndrome. A study on tongue and arm muscle thickness found that muscle loss can occur both in swallowing areas and generally [22], supporting the use of skeletal muscle indices to indicate muscle changes in swallowing regions. A cachexia-related mechanism could explain the systemic nature of this muscle loss.

The reviewed literature had several limitations. Notably, the studies in this review did not consider conditions like stroke, Parkinson's Disease, or dementia, which contribute to 75% of dysphagia cases in elderly patients [23]. Additionally, there is a risk of bias in some papers, particularly Amano et al., 2018, which failed to account for cancer type, potentially affecting the independence of cachexia-related dysphagia from tumour location. While the Food Intake LEVEL Scale and Functional Oral Intake Scale used in two studies were validated [24,25], the dysphagia assessment measures in the other studies lacked validation. Furthermore, the lack of consensus on cachexia definitions impacts

Table 3: Results

Author & Year	Cachexia Measurement Methods	Cachexia Definition	Dysphagia Measurement Methods	Dysphagia Definition	Results	Covariates Accounted For	Risk of Bias
(Kenny et al., 2019)	Height & weight obtained by medical notes or self-reported.	Body weight loss rate in 6 months ≥ 5% or body mass index < 20 kg/m(2) + in 6 months ≥ 2%. *(Fearon et al., 2011)*	Questionnaire, Cranial Nerve Examination	1. Concrete swallowing difficulties reported during case history, even if these were not observed during swallow trials 2. MASA score #177, MASA aspiration or dysphagia risk anything other than ''unlikely'' 3. FOIS score <7 4. Participant needed to use compensatory strategy *(Mann, 2002)* *(Crary et al., 2005)*	**2.1 (1.1-4.0)** *[P=0.033]* *Cachexia as a predictor of dysphagia*	Anorexia Cough Dysphonia Nausea Wheeze ECOG-PS Taste changes Setting (hospice or hospital) Dyspnoea Cognition Quality of life % Weight loss Health care team Patient location Health care provider HNO radiotherapy Early satiety	Low
(Amano et al., 2018)	Height & weight obtained by self-reported questionnaire.	Body weight loss rate in 6 months ≥ 5% or body mass index < 20 kg/m(2) + in 6 months ≥ 2%. *(Fearon et al., 2011)*	Questionnaire	Patient-Generated Subjective Global Assessment (PG-SGA) *(Bauer et al., 2002)*	**0 (0-2)** *[P=0.002]* *Non-cachexia patients presenting with dysphagia* **2 (0-5)** *[P=0.002]* *Cachexia/refractory patients presenting with dysphagia*	N/a	Moderate
(Lasheen and Walsh., 2010)	Height & weight obtained by medical notes or self-reported questionnaire.	Weight loss >10% of pre-illness body weight *(Blackburn et al., 1977)*	Questionnaire	Empirically derived clinical assessment based on conventional medical history taking. *(Walsh et al., 2000)*	**Prevalence of 28%** *[P<0.05]* *Dysphagia in patients with cachexia* **Prevalence of 12%** *[P<0.05]* *Dysphagia in patients with no weight loss*	Primary cancer site Gender ECOG Age	Low
(Wakabayashi et al., 2015)	C-reactive protein Skeletal muscle mass assessed by abdominal CT.	Skeletal Muscle Index (psoas area/height^2)	10-point observer-rating scale	Food Intake LEVEL Scale *(Kunieda et al., 2013)*	**1.8 (1.1-3.0)** *[P=0.018]* *Skeletal muscle index as a predictor of oral food intake*	Age Sex Albumin Barthel index Cancer stage Cancer type Vocal cord paralysis	Low

Table 4: Quality Appraisal – CASP Cohort Tool

	(Kenny et al., 2019)	(Amano et al., 2018)	(Lasheen and Walsh., 2010)
1. Did the study address a clearly focused issue?	Yes	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
3. Was the exposure accurately measured to minimise bias?	Can't tell	Can't tell	Yes
4. Was the outcome accurately measured to minimise bias?	Yes	Can't tell	Can't tell
5. (a) Have the authors identified all important confounding factors?	Yes	No	Yes
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	Yes	No	Yes
6. (a) Was the follow up of subjects complete enough?	n/a	n/a	n/a
6. (b) Was the follow up of subjects long enough?	n/a	n/a	n/a
8. How precise are the results?	Precise *(Narrow CIs / Low p values)*	Can't tell *(Wide CIs / Low p values)*	Can't tell *(No CIs given)*
9. Do you believe the results?	Yes	Can't tell	Yes
10. Can the results be applied to the local population?	Yes	Yes	Can't tell
11. Do the results of this study fit with other available evidence?	Yes	Yes	Yes
12. Does the study have implications for practice?	Yes	Yes	Yes

Table 5: Quality Appraisal – CASP Case Control Checklist

	(Wakabayashi et al., 2015)
1. Did the study address a clearly focused issue?	Yes
2. Did the authors use an appropriate method to answer their question?	Yes
3. Were the cases recruited in an acceptable way?	Yes
4. Were the controls selected in an acceptable way?	Yes
5. Was the exposure accurately measured to minimise bias?	Yes
6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
7. How large was the treatment effect?	Moderate
8. How precise was the estimate of the treatment effect?	Can't tell
9. Do you believe the results?	Yes
10. Can the results be applied to the local population?	Yes
11. Do the results of this study fit with other available evidence?	Yes

the overall strength of the conclusions. Nevertheless, it's important to note that, despite these variations, a consistent association between muscle loss and dysphagia was observed.

Dysphagia is well-documented as a consequence of age-related muscle wasting, known as sarcopenia20. Given that the mean ages in these studies ranged from 66 to 70, and the estimated prevalence of sarcopenia in patients aged 65 to 70 is around 14% [26], it's reasonable to consider that some patients might have experienced dysphagia due to sarcopenic muscle loss rather than cachexia. This is plausible, especially since only one of the selected studies took sarcopenia into account [20]. Research is needed to explore how the interplay between the cachectic mechanism of inflammatory muscle destruction and sarcopenic muscle loss impacts these associations, emphasizing the importance of controlling for sarcopenia in future studies.

The potential link between cancer cachexia and dysphagia suggests that markers of cachexia may signal the need for dysphagia assessment in patients with non-head and neck tumours. Unlike other muscle-wasting conditions like sarcopenia, there's evidence to indicate that cachexia is not associated with neuromuscular junction pathology [27]. In the absence of denervation, muscle weakness in cachexia might be solely attributed to intrinsic muscle degradation. If this holds true, the extent of skeletal muscle loss in cancer cachexia patients could directly indicate their dysphagia risk.

LIMITATIONS

This systematic literature review has several limitations. The requirement that the term "cancer" or related words be in the title of each paper may have excluded potentially relevant articles. The exclusion of non-English papers, pre-prints, and grey literature also raises the risk of missing pertinent studies. The lack of a second independent reviewer may introduce bias. The heterogeneity among the included papers, particularly Wakabayashi et al., 2015, which examined skeletal muscle index instead of cachexia, posed significant limitations. The use of odds ratios and prevalence reports made comparisons challenging. The studies had different designs: one case-control, two cross-sectional, and one analysis of previously reported cohort data. The use of varying CASP tools for cohort and case-control studies limited the strength of quality comparison.

CONCLUSION

The aim of this review was to explore the links between cancer cachexia and dysphagia in patients with tumours beyond the head and neck. Swallowing problems are common in cancer patients, yet they are often overlooked in non-head and neck cancers. This oversight can negatively impact patients' quality of life and increase mortality rates. The data gathered in this review suggest that cachexia is independently associated with dysphagia in cancer patients. While factors like sarcopenia, neurodegenerative diseases, or bias might contribute to these associations, there is a consistent trend in these studies. This review paves the way for future research into the mechanisms of cachexia-related dysphagia and their interactions with sarcopenia. The evidence also supports the use of cachexia-related muscle loss measures as indicators of dysphagia risk in patients with tumours outside the swallowing regions. Ultimately, a greater focus on this condition will enhance the early identification and management of dysphagia.

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Supplementary

Appendix 1: Sample Data Extraction Table

Bibliographical Information *(Title, author, year of publication, funding)*	**Objectives**	**Study Design + Methodology** (Sample size, inclusion/exclusion criteria, recruitment method)	**Exposure** *(Patient characteristics, cancer type & stage, other complications (e.g. dementia), treatments, setting, cachexia definition)*	**Outcome** *(Dysphagia definition, associated outcomes)*	**Results** *(relative risk and odds ratios)*	**Strengths and Limitations**
(Amano et al., 2018) **Eating-related distress in advanced cancer patients with cachexia and family members: a survey in palliative and supportive care settings** **Funding**: The Institutional Review Board approved this study (No. 1804008)	[1] to examine the severity of nutrition impact symptoms, which are to be palliated as part of nutritional support, in advanced cancer patients and the prevalence of eating-related distress among patients and their family members in palliative and supportive care settings, including outpatient services, palliative and supportive care teams, and the palliative care unit [2] compared these parameters between the following groups: (1) non-cachexia/pre-cachexia and (2) cachexia/refractory cachexia.	Type: Cross-sectional Population: Palliative care patients in Osaka City General Hospital (advanced cancer patients) Sample Size: N= 140 Recruitment Method: Primary palliative care physicians consecutively identified potential participants among patients, researchers approached patients and families and delivered questionnaires. If response was given, this was consent. Inclusion Criteria: (1) adult patients receiving palliative care, (2) patients diagnosed with locally extensive or metastatic cancer (including haematological neoplasms), (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–3, 4) no marked fluid retention, e.g., ascites, pleural effusion, and peripheral oedema, (5) capable of replying to a self-reported questionnaire, (6) awareness of the diagnosis of malignancy, and (7) no serious psychological distress recognized by the primary palliative care physician's interview Family members: 1) primary caregivers of patients meeting the inclusion criteria as above, (2) capable of replying to a self-reported questionnaire, (3) awareness of the diagnosis of malignancy, and (4) no serious psychological distress recognized by the primary palliative care physician's interview. Exclusion Criteria: - Methods: - Eating-related distress questionnaire - 9 symptoms evaluated: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and a feeling of well-being (ESAS-r tool) - Split into non/pre-cachexia and cachexia/refractory groups	Mean age: 66.3 (±11.1) Primary cancer types included esophageal (n = 55), lung (n = 13), gastric (n = 11), brain (n = 6), colon (n = 5), prostate (n = 5), hepatocellular (n = 2), thyroid (n = 2), pharyngeal (n = 2) and others (n = 10) Disease Extent: Metastatic n=484 (100%) Treatment Status: Pre-chemotherapy 8 (5.7%) Chemotherapy 89 (63.6%) Never treated/previous treatment 43 (30.7%) **Cachexia Definition**: (Fearon et al., 2011) Cachexia/refractory cachexia was a body weight loss rate (BWLR) in 6 months ≥ 5% or body mass index (BMI) < 20 kg/m2 + BWLR in 6 months ≥ 2%.	**Dysphagia Definition**: ➔ *Difficulty Swallowing* *Bauer J, Capra S, Ferguson M (2002) Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 56(8):779–785*	**0 (0-2)** *[P=0.002]* *Non-cachexia patients presenting with dysph* **2 (0-5)** *[P=0.002]* *Cachexia/refractory patients presenting with dysph* ***Conclusions**:* *(Another study saw dysphagia in 12% of patients with cancer cachexia)* • *"Patients with cachexia had significantly greater eating-related distress than those without cachexia."* • *"In addition, the present study showed that the severity of 8 symptoms, i.e., tiredness, drowsiness, lack of appetite, early satiety, diarrhea, abnormal taste, difficulty swallowing, and feeling of well-being, were significantly greater in the cachexia/refractory cachexia group"*	**Strengths**: • Validated definition of cachexia **Limitations**: • Body weight measurements may have underestimated the frequency of cancer cachexia in patients who had gained weight due to fluid retention and overestimated it in overweight or obese patients • Items related to distress originating from the relationship between patients and their families may have been underestimated • A main limitation is that the measures for eating-related distress in both advanced cancer patients and their family members have not been previously validated

The Cancer Anorexia-Cachexia Syndrome: Myth or Reality? *(Lasheen and Walsh., 2010)*	
1. Did the study address a clearly focused issue?	Yes. It is unclear how to define CACS and if it is a distinct clinical disorder. The researchers evaluated whether CACS is a distinct clinical entity, identified the clinical features and assessed their impact
2. Was the cohort recruited in an acceptable way?	Yes. These participants are representative of the palliative care cancer patient population. The participants were not recruited, as this is a post hoc analysis of a cohort. This is however an acceptable method given that the data is all present for a reasonable proportion of this cohort. Only symptoms with an overall prevalence of over 5% were analysed, which limited the exclusion of patients without uncommon symptoms.
3. Was the exposure accurately measured to minimise bias?	Yes. Self-reported weight measurements were confirmed by medical documentation. Appropriate definition of cachexia was used, with over 10% weight loss being used in other studies. The study was produced before the international consensus on cachexia definition but employs a frequently used cachexia definition at this time.
4. Was the outcome accurately measured to minimise bias?	Can't tell. "Data was collected using an eight-page questionnaire". The validity or reliability of this questionnaire is not addressed. Even within the paper that originally reported these data, there is no indication that this is a validated diagnosis of dysphagia. The questionnaire was "empirically derived", however its specificity with regards to dysphagia is questionable.
5. (a) Have the authors identified all important confounding factors?	Yes. Primary cancer site and a number of other contributing variables are mentioned in the statistical analyses.
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	Yes. Regression was performed with age, gender, ECOG, primary cancer site, group CACS, group A, group WL, and group N.
6. (a) Was the follow up of subjects complete enough?	n/a
6. (b) Was the follow up of subjects long enough?	n/a
7. What are the results of this study?	Dysphagia significantly more common in the CACS group when compared to group A and group WL ($P<0.01$).
8. How precise are the results?	Can't tell. The results all have a precise p-value (all $p<0.05$). Confidence intervals are not given.
9. Do you believe the results?	Yes. The p-value is low, and confounders have been accounted for. The study methods are solid and should support the accuracy of these results.
10. Can the results be applied to the local population?	Can't tell. The questionnaire used by the study is not clear and therefore may not be validated or accessible for other populations. Cachexia definition should be applicable to local populations; however the international consensus may serve as a more reliable measure of cachexia.
11. Do the results of this study fit with other available evidence?	Yes. conditions and dysphagia, however, this paper does not focus on the mechanism involved in its discussion section.
12. Does the study have implications for practice?	Yes. More research is needed to distinguish this syndrome. A comprehensive validated CACS assessment instrument is required in the future. This study suggest that CACS is a subset of cachexia and includes 9 other symptoms (which could in fact be caused by cachexia itself however).

Appendix 3: Sample Quality Appraisal – CASP Case Control Checklist

Skeletal muscle mass is associated with severe dysphagia in cancer patients (Wakabayashi et al., 2015)	
1. Did the study address a clearly focused issue?	Yes. No studies have reported the association between skeletal muscle mass assessed by abdominal CT and severe dysphagia. Focus is justified.
2. Did the authors use an appropriate method to answer their question?	Yes. Appropriate method of identifying the relationship, as researchers can identify those with and without dysphagia by means of clinical assessment and determine the effects if exposures from here
3. Were the cases recruited in an acceptable way?	Yes. Cases were identified by their diagnosis of cancer and referral for speech therapy to treat dysphagia by Yokohama City University Medical Center. These are representative of cancer patients admitted to this medical center. All patients who fitted the cancer and dysphagia rehabilitation criteria where included. The exclusion of patients who had undergone CT for diagnostic purposes is justified. No selection bias is evident through this approach. Cases were diagnosed for accuracy.
4. Were the controls selected in an acceptable way?	Yes. Controls were recruited in the exact same method as above and were defined as those who did not have dysphagia at the time of discharge. This was the only differentiating factor about the controls.
5. Was the exposure accurately measured to minimise bias?	Yes. Skeletal muscle mass was measured appropriately by CT. Measurements were consistent with cases and controls.
6. (a) Aside from the experimental intervention, were the groups treated equally?	Yes. Patients were all subject to the same measurement procedures. They are all admitted to the same hospital and referral scheme, however socio-economic factors are no investigated.
6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes. Skeletal muscle index was associated with dysphagia after adjustment for age, gender, serum albumin, haemoglobin, cancer type and stage and vocal cord paralysis. This negates factors which may have caused dysphagia.
7. How large was the treatment effect?	Moderate. Forced entry logistic regression analysis showed that the skeletal muscle index (odds ratio [OR] 1.829; 95% confidence interval [CI]1.107–3.022; P = 0.018) was associated independently with oral food intake at discharge. The only significant adjustment was BMI, which made a difference of 0.508 to the OR [P<0.05] which is somewhat related to skeletal muscle mass. However the association was still significant outside of this.
8. How precise was the estimate of the treatment effect?	Can't tell. Relatively narrow CI intervals, however P values only
9. Do you believe the results?	Yes. All potential confounders are accounted for (bar cachexia, which is itself related to skeletal muscle mass and therefore linked). Associations are relatively strong and possible mechanisms are explored in the discussion to back up findings.
10. Can the results be applied to the local population?	Yes. Similar measurements could be performed in a local setting, provided the participants can be recruited by means of referral.
11. Do the results of this study fit with other available evidence?	Yes. The findings are supported by other papers as discussed in the discussion section.

Review of the Dietetic and MDT Management of Cystic Fibrosis

AOIFE TWOMEY

Abstract

INTRODUCTION: Cystic Fibrosis (CF) is an autosomal recessive disorder due to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene leading to abnormality of chloride channels in mucus and sweat producing cells. The respiratory system (lungs) and digestive system (GIT) are primarily impacted, leading to life threatening complications (Rafeeq and Murad, 2017). Ireland has the highest incidence of CF in the world. Approximately 1 in 19 Irish people are said to 'carry' one copy of the altered gene that causes CF (Cystic Fibrosis Ireland, 2023). More than 1900 mutations of CF have been identified (Rafeeq and Murad, 2017).

METHODS: Articles for review were sourced from the academic database PubMed. Results were screened using PICOS criteria, focusing on dietetic management of CF. Papers dating back as far as the 1980's were included in the review due to their continuing relevance in CF treatment today.

RESULTS: Initial database searches identified 61 results, which were then screened for relevance to the objectives of this review. Treatment of CF requires a multi-disciplinary team approach, for which Nutrition and Dietetic management is integral. Lifelong management of CF includes pharmaceutical treatment to manage symptoms, case specific diet and lifestyle therapy, management of complications and co-morbidities, and novel therapies such as CFTR modulators.

CONCLUSION: The identification of the faulty CFTR gene that causes CF was an important step in managing the disorder, yet has not led to a cure for the condition. Life expectancy for patients with CF has steadily improved during the last three decades, with medical management of symptoms and advances in CF therapies. Complications associated with the condition are treated on a case-by-case basis due to complexity of symptoms and individuality of the condition. Dietetic management includes a high calorie, high salt, and high protein diet and routine monitoring for changes in symptoms and

nutritional deficiencies.

KEYWORDS: Cystic Fibrosis, dietetic management, CFTR gene, physical activity in cystic fibrosis, prevalence of cystic fibrosis in Ireland

Introduction

Cystic Fibrosis is an autosomal recessive disorder due to mutations in the CFTR gene leading to abnormality of chloride channels in the lungs and sweat producing cells. Respiratory system and GIT are primarily involved, but eventually multiple organs are affected leading to life threatening complications. CF management requires drug therapy, physiotherapy, and nutritional support.

Life expectancy for patients with CF has steadily improved during the last three decades, and death in childhood is now uncommon. Nutrition is a critical component of the management of CF.

Nutritional status is directly associated with both pulmonary status and survival (Dodge et al.,

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2007). Poor clinical outcomes are often associated with undernutrition (Kalnins and Wilschanski, 2012).

Complications of CF, including liver disease and CF-related diabetes, pose further challenges to medical management of the condition. Glucose intolerance and diabetes affect at least 25% of CF adults. The diabetes differs from both types 1 and 2 diabetes mellitus, but it inversely correlates with prognosis (Dodge et al., 2007). The CFTR gene is located at 7q31.2. More than 1900 mutations have been identified of which 'F508del' (deletion of three bases coding for phenylalanine at the 508th position) is the most common (Rafeeq, 2017).

Prevalence and testing

CF is more common in adults than children in countries with well-developed healthcare systems. The number of adults continues to increase and will further increase if the new CFTR modulators are disease modifying. Most of the complex morbidity and almost all the mortality of CF occurs in adults. It will increasingly follow this pattern even with new effective modulator therapies. Maintaining good quality of life including social functioning and maximizing survival for adults are the key priorities.

This requires a highly knowledgeable and adaptable multidisciplinary team, which, though focused on maintaining lung health, requires an increasing range of other disciplines and specialties to maximize well-being (Elborn, 2019).

All newborn babies in Ireland are now screened for CF as part of the newborn heel prick test carried out shortly after birth. If the screening test suggests a child may have CF, additional tests are carried out to confirm the diagnosis. For example, a sweat test measures the amount of salt in sweat, which will be abnormally high in someone with CF. Alternatively, a genetic test sample of blood or saliva is checked for the faulty gene that causes CF. These tests can also be used to diagnose CF in older children and adults who didn't have the newborn test (Fitzgerald et al., 2020).

Complications of Cystic Fibrosis

CFTR protein enables chloride to pass through the mucus producing cells where water follows and mucus becomes thin. Defective CFTR results in thick and sticky mucus obstructing the pathways (Cystic Fibrosis Foundation, 2016), leading to serious bacterial lung infections. Neutrophil elastase (NE) is a major inflammatory protease released by neutrophils and is present in the airways of patients with CF. Although NE facilitates leukocyte transmigration to the site of infection and is required for clearance of Gram-negative bacteria, it also activates inflammation when released into the airway milieu in chronic inflammatory airway diseases (Voynow and Shinbashi, 2021). In the GIT, the mucous plugs obstruct the canaliculi of pancreas and gall bladder duct preventing enzyme and bile flow into duodenum triggering malabsorption and digestion abnormalities (Houwen, 2010).

CF is a significant burden to both the sufferer and their family, requiring regular review of symptoms, medical testing and treatments to manage symptoms and maximise quality of life. Common complications of the condition include impaired mucus clearance in the lungs, leading to chronic bacterial infections in the lungs, bronchiectasis, dehydration, damage to both the endocrine and exocrine pancreas which results in fat malabsorption, macro and micronutrient deficiencies and often diabetes. CF can also damage the hepatobiliary system, resulting in cholestasis, cholelithiasis, liver cirrhosis and hypertension. Colon cancer is also common in people with CF, as is Osteoporosis.

Fertility problems are common, particularly in men with CF. It is possible for women with CF to have children, but men won't be able to father a child without fertility specialists (Konrad et al., 2022).

Abdominal pain is a very common symptom in CF and may affect nutritional status as the patient fails to reach required intakes (Kalnins and Wilschanski, 2012). Abnormal bile salt metabolism, liver disease, mucosal absorptive abnormalities and short bowel syndrome after intestinal resection in the neonatal period may all contribute.

Stool energy losses account for 10% of gross energy intake in CF patients, three times higher than normal. Sodium losses are important, and subclinical salt depletion can result in growth impairment, particularly in infancy. Factors associated with reduced appetite include chronic respiratory infection, and other

complications of CF such as distal ileal obstruction syndrome and gastro-oesophageal reflux result in oesophagitis, pain, and vomiting (Murphy et al., 1991).

Dietetic Managment of CF

A range of treatments can help control the symptoms, prevent, or reduce complications, and make CF easier to live with. MDT involvement is needed to detect and treat changes and complications with the condition. Malnutrition is both a frequent feature and a comorbidity of CF, with nutritional status strongly associated with pulmonary function and survival. Nutritional management is therefore standard care in CF patients (Turck et al., 2016).

A diet composed of 35%–40% calories from fat is recommended in order to meet the energy demands of those with CF (Kalnins and Wilschanski, 2012). This is a higher fat diet than the European Food Safety Authority (EFSA) 2010 recommendation for non-CF general population, which is 20% to 35% daily energy from fat. The nutritional problems in CF are multifactorial, and include increases in intestinal losses, energy requirements, and urinary glucose losses. One or more factors almost invariably coexist in combination with an inadequate energy intake. Malabsorption in CF mainly results from maldigestion secondary to pancreatic insufficiency.

Malabsorption is characterised by foul smelling, loose, pale stools. The degree of fat malabsorption is usually taken as the marker of intestinal malabsorption. The gold standard for measuring fat absorption is an assessment of the fat excretion over 3 days and its relation to dietary fat intake over the same time period (Sinaasappel et al., 2022).

People with CF struggle to gain weight due to high nutrient losses and malabsorption. Dietetic management centres on a high energy, high fat/high protein diet including foods such as full cream milk, full fat cheese, meat, eggs, full fat butter, bread, and cream, as well as sources of polyunsaturated fats like oily fish, tailored to the individual with consideration for lifestyle, clinical conditions/co-morbidities, nutritional state, social/financial circumstances, dietary beliefs and attitudes, appetite, and activity levels. Nutritional counselling should always be age appropriate. Dieticians develop education programmes and information booklets and teaching materials to support each patient (McDonald et al., 2021).

Pancreatic Enzyme Replacement Therapy (PERT), the most common form being Creon®, is administered at an appropriate and individualised dose with every meal and snack to improve fat absorption and prevent steatorrhea (oily, fatty stool). Requirements can vary widely from 500-2,500 IU lipase per gram of fat (Conway, 2008). Dose should be monitored and adjusted to the fat content of meals and individual symptoms. There are now three preparations which are currently approved: Creon®, Zenpep®, and Pancreaze® (Kalnins and Wilschanski, 2012). In the 1940's, prior to the development of effective PERT, a low-fat diet was prescribed to patients with CF to control side effects such as malabsorption and steatorrhea. After enteric coated pancreatic enzymes were developed in the 1980's, a high fat diet was recommended for CF management, which improved growth and weight stabilisation. These enzymes resist stomach acid and are only released when the more alkaline environment of the upper small intestine is reached. While enzyme therapy for those with pancreatic insufficiency does allow for normal growth and weight gain in most individuals with CF, they do not completely correct nutrient malabsorption.

A broad recommendation for energy requirements in CF has been stated to be approximately 110- 150% and even up to 200% of those required by healthy individuals of the same age, sex, and size (Turck et al., 2016).

People with CF are prescribed NSAIDs, antibiotics, and laxatives to treat symptoms of inflammation, bacterial infections, and constipation respectively. Routine biochemical monitoring, usually annually, is needed to assess status of fat-soluble vitamins (A, D, E and K) and minerals such as zinc and iron due to risk of deficiencies. Albumin and prothrombin are also routinely measured (MacDonald, 1996). These nutrients are often supplemented. Calcium and vitamin D supplements are administered to prevent osteoporosis due to malabsorption and fecal losses. Vitamin D deficiency has been reported in 22% of infants at diagnosis and suboptimal levels reported in more than 90% of older patients (Turck et al., 2016)

Normally there is no need to recommend additional sodium, but salt depletion can occur in hot weather, through physical exercise causing increasing sweating, and in infancy if an infant is on a normal low electrolyte formula. Routine salt supplementation may be needed during hot weather and in all infants on normal infant formulas (MacDonald, 1996).

Most infants with pancreatic insufficiency thrive on a normal energy intake of 100-130 kcal/kg in adjunct with pancreatic enzymes. Breastmilk is suitable for infants with CF. It contains lipase, long chain polyunsaturated fatty acids, provides some immunological protection against infection, and may be psychologically better for the mother (MacDonald, 1996). Infants on breast milk and pancreatic enzymes grow and gain weight appropriately with near zero z scores (Holliday et al., 1991). One possible concern is the possibility of electrolyte depletion on this low sodium milk, so routine sodium supplements are administered to all breastfed babies and some formula fed babies and urinary electrolytes are monitored if weight gain is poor (Laughlin et al., 1981).

Breastfeeding has been shown to be protective for the infant with CF. Breastfed compared with formula-fed infants with CF had improved lung function and a reduced incidence of infections in the first 3 years of life in a study from Italy (Colombo, 2007). Breast milk can provide complete nutritional support for infants with CF for the first 4–6 months of age, though supplemental energy may sometimes be required by fortifying a portion of the breast milk feeds with formula (Kalnins and Wilschanski, 2012).

Lung transplant (LT) is a treatment option for some people with end stage CF which can offer a survival benefit and improved quality of life (Yeung et al., 2020). Optimising nutritional status pre- transplantation is recommended as it can improve perioperative and post LT survival outcomes (Lederer et al., 2009).

Diabetes and CF

HBA1C is monitored routinely at appointments. Cystic Fibrosis Related Diabetes (CFRD) can occur. The primary aetiology is relative insulin insufficiency secondary to destruction of pancreatic islets. The diabetes is non-ketotic, has a slow onset, but is usually insulin dependent. No clear guidelines have been issued on ideal dietary management for patients with both CF and diabetes, although advice should be tailored according to the severity of the CF. The prevalence of CFRD increases with age and affects approximately 2% of children, 19% of adolescents and 40-50% of adults (Grandos et al., 2019).

Providing optimal nutrition for the CF patient is still of paramount importance and any dietary restriction should be avoided. Where possible, sugar free soft drinks, exchange glucose polymer supplements for fortified milk supplements, and some unrefined carbohydrate is given at regular meals, snacks, and bedtime. With the exception of drinks, simple sugars are not prohibited, but intake is encouraged alongside unrefined carbohydrates. Diabetic control is improved by alterations in insulin treatment rather than imposing dietary restrictions which may adversely affect nutritional status (MacDonald, 1996). Patients with CFRD should follow the same dietary advice as CF patients without CFRD (Turck et al., 2016).

Exercise and CF

Physical activity (PA) is associated with a number of potential benefits in the management of CF including positive effects on lung function (Schneiderman et al., 2014), mucociliary clearance (Dwyer et al., 2019), bone health (Garcia et al., 2011) and hospitalisation frequency (Cox et al., 2016).

Declining levels of exercise leads to low cardiorespiratory fitness, which is a strong, independent predictor of mortality in patients with CF. As a result, exercise training has become a commonly accepted form of treatment for patients with CF (Burnett et al., 2020).

Novel CF treatment

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators are small molecules that directly impact the CFTR protein, improving the function of the CFTR chloride and bicarbonate channel. Beginning in 2012 with the Food and Drug Administration approval of the first CFTR modulator, Ivacaftor, this class of medications has had largely positive effects on many outcomes in people with CF,

including lung function, growth, and other clinical parameters (Goetz and Savant, 2020). A limitation of this novel treatment is that it only works when a specific mutation is present and is very expensive, so it is not suitable for all people with CF.

Discussion

Treatment of cystic fibrosis has advanced greatly in recent decades, with better understanding of the condition and advances in medicine and medical technology. Life expectancy has increased, and quality of life has improved. The significant number of CF mutations suggests that a range of specific CFTR modulator treatments may be required. There is a critical need for further research of the genetic condition, of the medicines and biotechnology interventions, and to establish clear guidelines for the MDT medical and dietetic treatment of the differing mutations of CF. With increases in numbers of adults with CF, the health system must adapt services to this demographic shift. Patient empowerment principles potentially lend themselves to cystic fibrosis care, particularly in adults. A randomized controlled trial of a 10-week home-based behavioural nutrition intervention, "Eat Well with CF," was carried out by Registered Dietitians and nutrition researchers to assess patient understanding of cystic fibrosis management. Outcome measures over 6 and 12 months were compared between the intervention group (n=34) and a standard care control group (n=34). This study revealed gaps in basic nutrition knowledge and skills, inadequate knowledge of diet-disease links and pancreatic enzyme replacement therapy (Watson et al., 2008), indicating the efficacy of such programmes, in adjunct with individualised medical and dietetic care to manage the diverse needs of the growing population of adults with CF.

Conclusion

Current CF treatments focus on symptom management, regularly monitoring and adapting treatment to disease progression to maximise quality of life. Medical advice and treatment are case specific and require an MDT approach, in which the dietician plays a crucial role. Nutritional support and advice must be tailored to meet the changing clinical and psychosocial needs of people with CF.

Declaration of Competing Interest

No competing interests to declare.

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Exploring the Biopsychosocial Model for Evaluation of an Acutely Suicidal Patient with Co-occurring Borderline Personality Disorder and Substance Misuse: A Case Study

STEN KAJITANI, DR. DAYANANDA SIDDAIAH

Abstract

BACKGROUND: Borderline Personality Disorder (BPD) is a significant public health concern, affecting an estimated 28,725 individuals in Ireland with considerable associated costs. Despite its complexity, the biopsychosocial model offers a comprehensive approach, enabling clinicians to integrate predisposing, precipitating, perpetuating, and protective factors when understanding and managing BPD.

OBJECTIVE: This report presents a case study of a 35-year-old woman with a background of BPD and substance abuse, detailing her biopsychosocial formulation during an episode of acute suicidal ideation.

METHODS:: The case entailed a thorough history and clinical examination, focusing on the biopsychosocial model's 4P causal framework: predisposing, precipitating, perpetuating, and protective factors.

RESULTS: This Predisposing factors were abundant, including family history of mental health disorders and personal history of trauma. Precipitating factors were multi-faceted, encompassing biological vulnerabilities from alcohol abuse and significant recent social stressors, such as unemployment, eviction, custody battles, and bereavement. Perpetuating elements revolved around ongoing legal challenges and deep-seated feelings of guilt. However, protective factors were also present: no co-existing medical conditions, an eventual stable mood post-treatment, and engagement in therapeutic activities, including mindfulness interventions.

CONCLUSION: This case underscores the value of the biopsychosocial model in psychiatric patient care, highlighting its potential to uncover individualized nuances in classic presentations. Embracing this model can optimize holistic care, underscoring its imperative utility in clinical practice.

Case Background

Borderline Personality Disorder (BPD)[1] poses a significant challenge in Ireland, affecting around 28,725 individuals and generating an estimated annual cost of €311.5 million[2]. This dual impact, both personal and financial, underscores the pressing need for a comprehensive approach to address BPD effectively. In this context, the application of the biopsychosocial model offers a promising framework for understanding and managing this complex disorder.

While personality disorders are generally understood to be influenced by unchangeable genetic

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factors, more contemporary literature emphasizes the importance of considering a broader range of factors that contribute to these disorders[3–6]. The biopsychosocial model, with its 4P causal framework (predisposing, precipitating, perpetuating, and protecting factors), equips clinicians with a versatile toolset to navigate the intricacies of BPD. This approach enhances diagnostic precision, guiding tailored interventions and prognostic assessments by comprehensively addressing biological, psychological, and social aspects[7–10]. This holistic model recognizes that health and illness are influenced by biological, psychological, and social factors, allowing for a comprehensive understanding of individuals and their health conditions. Through its patient-centered focus, the biopsychosocial model emphasizes the importance of understanding patients' experiences, beliefs, and social contexts, empowering them to actively participate in their healthcare decisions. Furthermore, it promotes a preventive approach to healthcare by addressing not only biological factors but also psychological and social determinants of health, ultimately leading to better health outcomes and reduced healthcare costs in the long term.

In this case report, a specific patient's experience is examined to illuminate the practical application of the biopsychosocial model in the management of BPD. The goal of this paper is to demonstrate the value of the biopsychosocial model for identifying unique factors contributing to a disorder's complexity and how the model may be utilized as a primary source to focus management plans with.

Case Details

PRESENTING COMPLAINT:

A 35-year-old woman was referred from the Emergency Department to the Acute Psychiatry Unit following a failed suicide attempt. She reported symptoms of low mood, reduced sleep, and suicidal intent on a background of BPD, substance abuse, and suicide attempts that necessitated prior hospitalization in the Acute Psychiatry Unit.

HISTORY OF PRESENTING COMPLAINT:

The most recent suicide attempt involved the overdose ingestion of chlordiazepoxide (a long-acting benzodiazepine, which is a family of sedative drugs administered to treat stress, anxiety, and sleep disorders) and alcohol, which she immediately regretted. Her sister, a social worker, intervened when she attempted to hang herself with a bathrobe belt.

The patient's sister provided additional context, noting that the patient had been consuming 2 bottles of wine daily for the past four months, following their stepfather's death. The sister reported that the patient was heavily intoxicated at her own daughter's birthday party, where she had a nervous breakdown and an altercation with her daughter.

A retrospective exploration of the patient's childhood unveiled a history of instability, marked by parental conflicts, separation from her family, and a tumultuous experience in foster care after her father's rejection of her plea to live with him. Her initiation to alcohol at the age of 15 set the stage for a 15-year history of binge drinking, going up to 10 units of wine at least one day per month, and chronic suicidal ideation, often culminating in impulsive attempts, including wrist-cutting.

FAMILY HISTORY:

Her immediate family history showed a strong presence of alcoholism, schizophrenia, narcissistic personality disorder, anxiety, and depression.

SOCIAL HISTORY:

Despite experiencing an unstable childhood, the patient achieved academic success by earning her leaving certificate from school with distinction. She worked as a self-employed cleaner until her most recent hospital admission. She did not mind her job but was not especially passionate or satisfied with it. She worked by herself. She reported that she lost her clients since her admission and received social welfare payments for unemployment.

The patient had a history of physical, emotional, and sexual abuse from an ex-boyfriend, leading to diminished libido and a sense of unworthiness in relationships. She reported that she "used to be able to have fun" but now felt that she was "not good enough for anyone." "Everyone leaves me,'" she said.

The patient had never married and had three daughters, aged 4, 9, and 11, with different fathers. All the children resided with her, and the patient paid her mother to assist in her children's care during the patient's work hours. The patient lost custody of her youngest daughter during her most recent hospital

admission. She reported that she felt guilty for how her mental illness negatively affected her daughters' lives.

PREMORBID HISTORY:

The patient's sister described the patient as "always distressed" and "constantly threatening to kill herself". The patient felt isolated, distrusted most of her relationships, and coped through avoidance and binge drinking. The patient seemed to have insight into her own condition but limited engagement with mental health services. Her coping patterns suggested an insecure-resistant attachment style[11].

EXAMINATION:

Upon initial presentation, the mental state exam was significant for tearful and tired appearance with poor engagement or eye contact with the interviewer. The patient demonstrated a depressed mood and blunted affect. Cognition was intact. Physical examination revealed nil of significance.

Conducting a mental status examination constitutes a crucial component of psychiatric assessment, encompassing aspects such as appearance, behavior, motor activity, speech, mood, affect, thought process, thought content, perceptual disturbances, cognition, insight, and judgment. This examination serves to detect, diagnose, and track manifestations of mental disorders[13].

MANAGEMENT AND PLAN:

During her admission, the patient received chlordiazepoxide detoxification, fluoxetine (20mg), and zopiclone (7.5mg), which she tolerated well. Benzodiazepines are highly addictive, and a tapered detoxification approach is necessary to decrease withdrawal symptoms. Zopiclone, or other sleep aid, is routinely prescribed to patients to aid in insomnia that can occur in benzothiazepine withdrawal. Fluoxetine is a selective serotonin-reuptake inhibitor, also indicated to help with mood swings and anxiety related to withdrawal[12]. She also attended mindfulness therapies: gardening, sensory walks, and group art classes.

Upon discharge, the patient appeared cooperative, well-kept, and had a stable mood with anxious affect, with no suicidal ideation. Her plan included attending an alcoholic treatment program, securing emergency housing, and regular follow-ups at an outpatient psychiatric clinic.

Discussion

The significant predisposing factors the patient experiences are her family history of mental health disorders, her substance abuse, her history of sexual, emotional, and physical trauma, her experience in the foster care system, her insecure resistant attachment style, and her background of borderline personality disorder. The significant precipitating factors include alcohol abuse, her reduced sleep, her recent unemployment, her eviction from her home, the lost custody of her daughter, the recent death of a close relative, general financial stress, poor coping strategies, and fears of abandonment. Her perpetuating factors included her withdrawal from alcohol and illicit drugs, the ongoing legal battle for custody of her daughter, guilt from maladaptive coping strategies, and guilt from lack of presence in her children's lives. This patient's protective factors include her lack of other medical conditions, her positive response to pharmaceutical treatment, her moving her items from her old apartment, her application to a local alcoholic treatment program and emergency housing after she was discharged, her insight into her own diagnosis, and her positive psychological response to mindfulness therapies.

Conclusion

The formulation of this case demonstrates the applicability of the biopsychosocial model to psychiatric patient care. The patient provided a typical presentation of an acutely suicidal ideation, demonstrated by her recent premeditated attempt of suicide with a high lethality method (hanging) and her intent by leaving a goodbye message to her loved ones; in clinical practice these are the main determinants of a severe acute suicide attempt[14]. Unique dimensions of this case were exposed by using biopsychosocial formulation. Thus, it is imperative for mental health care providers to consider using the biopsychosocial model to provide more holistic care in their practice.

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GUARANTOR: Sten Kajitani

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Unraveling Pediatric Constipation: A Biopsychosocial Approach Toward a 2-year-old's Chronic Gastrointestinal Quandary

STEN KAJITANI, DR. FRANCES ENRIGHT

Abstract

INTRODUCTION: This case report unfolds the diagnostic and therapeutic journey of a 2-year-old girl with chronic constipation unresponsive to conventional laxatives, hinting at a possible underlying organic pathology amidst a complex familial and personal medical background.

METHODS: Utilizing a biopsychosocial model, a comprehensive assessment was conducted to delineate the predisposing, precipitating, perpetuating, and protective factors affecting the patient's gastrointestinal health. A multidisciplinary approach was employed to craft a tailored management plan involving the patient and her parents.

RESULTS: The application of the biopsychosocial model unveiled an intricate interplay of biological, psychological, and social factors contributing to the patient's persistent constipation. The multidisciplinary approach fostered a nuanced understanding and a patient-centered management plan, addressing not only the gastrointestinal symptoms but also the broader health and well-being of the child and her family.

DISCUSSION: The case accentuates the essentiality of transcending traditional biological examinations, embracing a holistic, patient-centered, biopsychosocial model, especially in pediatric patients with complex medical and familial backgrounds. It also underscores the need for an integrated, multidisciplinary approach for effective diagnosis and management in complex pediatric gastroenterological cases.

CONCLUSION: The case elucidates the paramountcy of a multidisciplinary, biopsychosocial approach in navigating complex pediatric gastroenterological cases, fostering an enriched discourse on patient-centered care and enhancing long-term health outcomes.

Case Background

This case outlines the diagnostic and therapeutic trajectory for a 2-year-old girl experiencing persistent constipation, unresponsive to conventional laxative regimens, suggesting a potential underlying organic pathology[1]. A familial history of Von Willebrand's Disease (VWD) and Cystic Fibrosis (CF), coupled with the patient's mild right-sided hemiplegia suspected to be cerebral palsy, enhances the clinical narrative. While chronic constipation in pediatrics often ameliorates with dietary and pharmacological interventions, this case underscores a subset resisting such standard remedies, necessitating a more nuanced diagnostic approach[2]. By exploring the predisposing, precipitating, perpetuating,

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and protecting factors through a biopsychosocial lens, this case illuminates a nuanced, patient-centric approach towards managing chronic constipation in pediatric patients, especially amidst a complex medical and familial milieu[3-4].

Case Details

PRESENTING COMPLAINT:

A 2-year-old girl presented 3 days ago with a 5/7 history of abdominal pain, distention, one time vomiting of feces, and straining during defecation with infrequent bowel movements, leading to significant discomfort and interrupted sleep.

The history of her presenting complaint involved 5 weeks of disimpaction protocol with 8 sachets of Movicol and 20 mL of Lactulose twice daily, which had no effect. Multiple laxatives and enemas were attempted without success. Her last stool was 4 days prior to presentation. Her background included a 22-month history of intermittent constipation, where she would have recurring 3-5 days of straining defecation with large hard balls with large streaks of blood on them, followed by 5-7 days of no bowel motion at all (i.e., impaction).

FAMILY HISTORY (FAMILY OF ORIGIN):

The family history reveals VWD Type I in the patient's mother and sister, CF in a cousin, and hip dysplasia in her father. The patient herself has tested positive for VWD prior to a rectal biopsy.

PERSONAL HISTORY:

The patient had a birth history of 36/40 induction of labor, delayed passage of meconium to Day 2/3, and jaundice in the neonatal period without requiring phototherapy. She had been living in a well-structured family environment but with a high-dairy, low-fiber/ protein diet primarily comprising white pasta, rice, and pizza. Her father was a smoker and smoked outside of the house.

PAST MEDICAL/ SURGICAL HISTORY:

The patient had a background of mild and improving right-sided hypertonia weakness with brisk reflexes, and a left hand preference secondary to suspected cerebral palsy. The patient's medical history is notably devoid of any invasive diagnostic or therapeutic procedures, including endoscopic evaluations or surgical interventions.

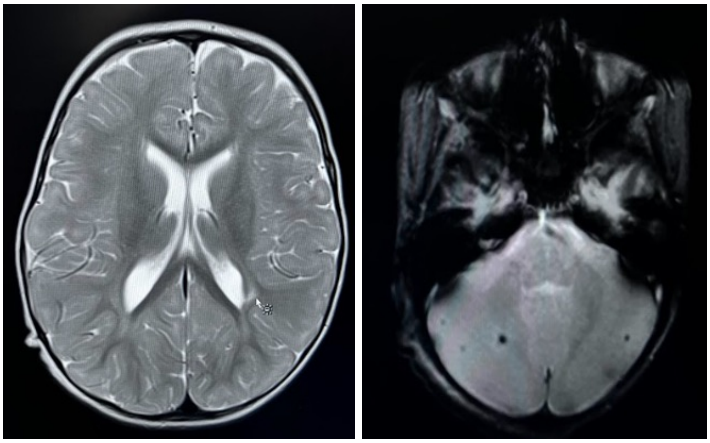

Figure 1/2: MRI Brain with Sedation

Findings: Overall myelination was appropriate.
Increased T2 signal noted in the left prior trigone territory involving the white matter. There was associated volume loss with tenting of the adjacent posterior horn lateral ventricle. There are six small foci of susceptibility artifacts in the posterior fossa. Small cortical focus of susceptibility artifact present in the right vertex.

Impression: There was evidence of left periventricular leukomalacia (PVL). Small foci of susceptibility artifact present consistent with microhemorrhages. Attribution to maternal production of antiplatelet antibodies at birth was ruled out by hematology.

PREMORBID HISTORY:

The patient was non-verbal but had manifested sounds indicative of her preferences. She was fully dependent on her caregivers for daily living activities. Unsuccessful attempts had been made to toilet train her.

The parents reported that the patient spent a significant portion of her time in her buggy or chair and received primary care physiotherapy. Her Gross Motor Function Classification System was 2. She was motivated to move by playing with her sister. Both parents were obese and lived a sedentary lifestyle. The parents were highly motivated to adopt a more balanced diet with fibrous foods and vegetables in their household.

Clinical Findings and Diagnosic Assessment

PHYSICAL EXAMINATION:

The patient, a 2-year-old girl, appeared active but irritable during the examination, likely secondary to abdominal discomfort. She was well-nourished, weighing

13.85 kg (between the 75th and 91st percentile) and a height of 85 cm (between the 9th-25th percentile). The patient was alert, oriented, and responsive to her name, though visibly uncomfortable. The abdomen was distended and hard on palpation. Bowel sounds were not assessed due to the patient's irritability and discomfort preventing complete examination, however loud gurgling and bowel sounds were reported by the parents. No scars, masses, or hernias were observed. The patient ambulated on her bum and knees, and demonstrated the ability to pull herself up onto a low bed.

IMAGING:

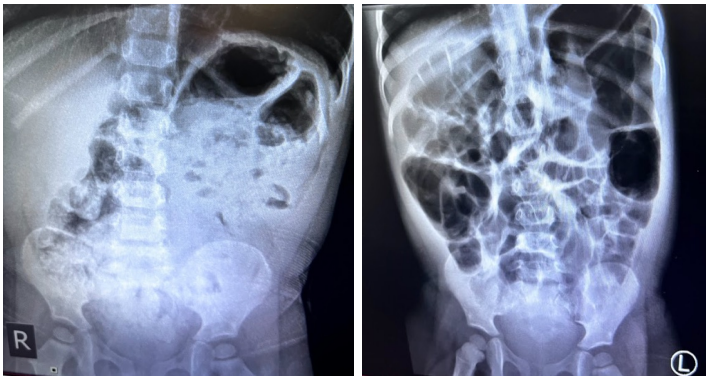

Figure 3/4:
(Left) The plain film abdomen (PFA) upon admission displayed pronounced fecal loading.

(Right) The empty PFA was acquired on the final day of hospitalization following a comprehensive disimpaction procedure.

PFA was prompted by the patient's complaint of abdominal discomfort and to confirm disimpaction efficacy. The investigation revealed that the reported discomfort could be attributed to gas production resulting from lactulose administration.

MANAGEMENT:

The disimpaction protocol included oral Lactulose (30mL initially, 20mL later twice daily), Phosphate Enema on admission (60mL), and Movicol Paed (8 sachets/day until clearout achieved). Picolax (2mg/kg once on admission) was attempted in desperation, albeit unsuccessfully.

Following disimpaction, the maintenance regime consisted of Microlax Enema (5mL) as needed, Movicol Paed (2 sachets) as needed, Dulcolax (3-5mg) twice weekly, and Paracetamol (15mg/kg) as needed. Patient was readmitted twice for further disimpaction. Patient currently refuses oral intake of Movicol and is now allowed a Nasogastric (NG) tube for administration of 8 sachets/day. Recent CF screening test using a heel prick was negative. Recent hip x-ray was normal. Patient awaits a Barium Enema procedure (CUH) and rectal biopsy (Crumlin Hospital) for suspected Hirschsprung's disease. Patient is awaiting surgical consultation as 2-day meconium suggested bowel motility and/or structural impairment.

Differential Diagnosis

1. Hirschsprung's Disease (HD)[5,6]
2. Chronic Functional Constipation (CFC)[6,7]
3. Medical causes e.g. Hypercalcaemia, Hypothyroidism, Renal Tubular Acidosis, Pyruvate Dehydrogenase Deficiency (PDD) [8-11] complicated by constipation
4. Cystic Fibrosis[12]
5. Von Willebrand Disease[13]
6. Anal stenosis[14]

Discussion

This case highlights the necessity of a multidisciplinary approach in addressing chronic pediatric constipation, especially when resistant to standard treatments. Utilizing a biopsychosocial formulation model, it delves into the intertwined factors affecting the patient's condition[3,4]. Despite the challenge posed by the child's irritability during examination, the case stresses the importance of an integrated care plan. This includes collaboration among pediatric generalists, pediatric surgeons, gastroenterology nurse-led resources like www.eric.org.uk and a poo passport, disability specialists, hematologists, physiotherapists, dietitians, and parents[1,2,15].

Addressing dietary habits, fostering an active lifestyle, and providing family education are also critical to improve the quality of life for the patient and her family.

Conclusion

This case underscores the paramountcy of a multidisciplinary, biopsychosocial approach in unraveling and managing complex pediatric constipation. It accentuates the necessity of transcending conventional pharmacological interventions to encompass a holistic understanding of the patient's biological, psychological, and social realms, thereby fostering a more efficacious, patient-centered management paradigm.

ETHICS APPROVAL:

Written informed consent for the case report was obtained from the patient's guardians.

CONFLICT OF INTEREST:

No conflict of interest to declare.

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GUARANTOR: Sten Kajitani

Table 1: This table elucidates the interplay of biological, psychological, and social factors across predisposing, precipitating, perpetuating, and protective dimensions, offering a comprehensive biopsychosocial formulation of the patient's chronic constipation..

Factor Type	Biological	Psychological	Social
Predisposing	• Family history of Cystic Fibrosis • History of mild hemiplegia secondary to suspected cerebral palsy or PVL. • Delayed passage of meconium	• Early onset of constipation potentially impacting emotional response to discomfort and treatment.	• Possible Family preferences for a sedentary lifestyle • Father was a current smoker; chemicals from cigarette smoke absorb to clothes / skin / hair
Precipitating	• High dairy, low fiber/protein diet contributing to onset of constipation.	• Possible withholding secondary to anal tears and this will delay toilet training.	• Patient's non-verbal cues leading to miscommunication for when she needs to defecate; parents mistook withholding behavior as straining
Perpetuating	• Resistance to first-line laxatives prolonging the constipation.	• Ongoing discomfort and sleep interruptions affecting the patient's desire to move and play	• Unfamiliar environment in the hospital, disrupting routine
Protecting	• Up to date on all vaccinations. • Access to medical care and medications.	• Family support and willingness to seek medical care.	• Play with sister • Parents motivated to improve household diet

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Harmonizing the Healing of Hand Trauma in a Piano Teacher: A Case Report on Pain Management in Ireland and Utilizing Butterfly Ultrasound for a Brachial Plexus Nerve Block

STEN KAJITANI, DR. BRIAN O'DONNELL, DR. QUENTIN JEANTET

Abstract

INTRODUCTION: This case report outlined a specialized surgical technique designed for the restoration of intricate hand functionality after a complex hand injury. It also highlighted the use of Butterfly iQ+ and its integration with iOS devices for teaching ultrasound techniques during the administration of a brachial plexus nerve block. Finally, concerns regarding pain management protocols in Ireland were raised.

CASE DETAILS: A 58-year-old piano teacher presented with a significant hand trauma. The restoration of intricate hand functionality essential for her profession as a piano teacher was a central concern. Her treatment included surgical exploration and wire fixation of the fractures. The application of Butterfly Ultrasound played an interesting role as an educational tool in anesthetic administration.

DISCUSSION:: The case presented significant challenges in postoperative rehabilitation, necessitating an adjustment to a more conservative approach due to the patient's high pain levels. This adjustment highlighted gaps in pain management and anesthetic care, especially during the transition from hospital to home care, revealing broader issues in Ireland's rehabilitation systems. The postoperative prescription of Oxycontin was inconsistent with established guidelines, pointing to a need for improved integration between primary and tertiary care.

CONCLUSION: This case underscored the importance of patient-specific, adaptable management strategies in trauma recovery. It showcased the potential role of Butterfly Ultrasound in clinical settings for anesthetic guidance and educational purposes. Finally, the report further prompted a broader dialogue on the improvement of pain management practices, particularly concerning the rise in opioid prescriptions in Ireland.

Case Background

This case report discussed a 58-year-old piano teacher's severe hand injury management, emphasizing the need for tailored surgical approaches to restore function for her professional piano playing[1,2]. The Butterfly iQ+'s seamless integration with iOS devices demonstrated its educational value as a "Point of Care" Ultrasound (POCUS) system in teaching ultrasound techniques during the administration of a brachial plexus nerve block[3–9]. Finally, the need for improved postoperative pain management to facilitate patient comfort and rehabilitation could not be more stressed[10]

Case Details

PRESENTING COMPLAINT:

A 58-year-old right-handed female piano teacher presented to the Hand Trauma Clinic at Cork University Hospital (CUH) with a referral from the CUH Emergency Department in the spring of 2023 after a fall on her outstretched hand that injured her right hand.

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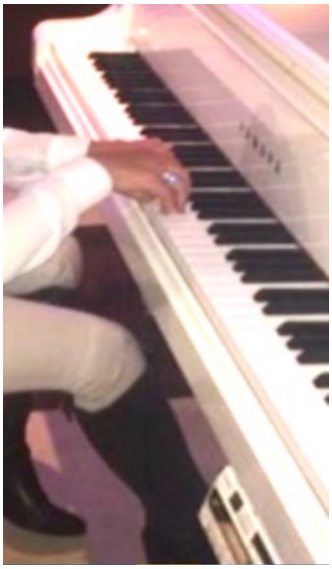

Figure 1: The patient's healthy hands minutes before the trauma

HISTORY OF PRESENTING COMPLAINT:

The patient tripped over the door threshold right before she was going to conduct a graduation service concert. When the patient fell, she hyperextended her middle finger while her other fingers were at flexion, causing a proximal interphalangeal (PIP) dislocation of her middle finger, where the proximal phalanx broke through the skin, as well as fracturing the proximal phalanges of her ring and little fingers. She complained of 10/10 pain in her fingers with loss of sensation on the palmar aspect of her distal middle phalanx. Upon presenting to the CUH Emergency Department, she was given 3mL methoxyflurane to inhale before reducing her middle PIP joint, which restored sensation and movement with intact peripheral pulses. Her hand was bandaged and splinted before she was referred to the Hand Trauma Clinic, where she was admitted for surgical exploration under anesthesia for her middle PIP joint as well as wire fixations of her 4th and 5th proximal phalanx fractures.

PAST SURGICAL HISTORY:

The patient's relevant surgical history included a successful percutaneous pinning of a left little finger fracture 30 years ago, which resulted in full function.

PAST MEDICAL HISTORY:

+Postmenopausal. +Presbyopia. No Hypertension, No Hyperparathyroidism, No Diabetes, No Osteoporosis.

MEDICATIONS:

Emergency Department (ED):

- Oxynorm 8 mg PO @ 19:30 and 5 mg PO @ 13:50
- Ibuprofen 400 mg PO @ 13:20 Tetanus IM @ 13:30
- Cefuroxime 15 g IV @ 13:30

On the ward:

- Paracetamol 1 g PO QDS 6 hrs.
- Ibuprofen 400 mg PO TDS 6hrs
- Lansoprazole 30 mg PO OD
- Clexane 40 mg S/C OD
- Oxynorm 5-10 mg PO

Post Operation:

- Paracetamol 1 g PO QDS 6 hrs
- Ibuprofen 400 mg PO TDS 6hrs
- Oxynorm 5mg every 4 hours 1 week
- Nexium 20mg Q.D.
- Amoxicillin 3 a day for 1 week Oral

ALLERGIES:

The patient reported that she had no known drug allergies, but she reported that she did not tolerate Tramadol well, and complained of painful swelling of the joints with Tramadol.

FAMILY HISTORY:

Family history was unremarkable.

SOCIAL HISTORY:

The patient was a piano teacher and had never smoked. She would take 1-2 alcoholic drinks on weekends. The patient lived with a partner. She used glasses to read. The patient felt mildly anxious about surgery, which she planned to alleviate by listening to classical piano music during the operation.

REVIEW OF SYSTEMS:

The patient had a light bruise on right cheek and an abrasion on her right knee, and a 4/10 sore shoulder. The patient denied fevers, lethargy, anorexia, weight loss, headaches, dizziness, or weakness.

Examination

On physical examination, the patient's right hand had a laceration on the palmar aspect of her middle finger along the PIP joint line with notable redness an swelling along the 3rd-5th proximal phalanges. The

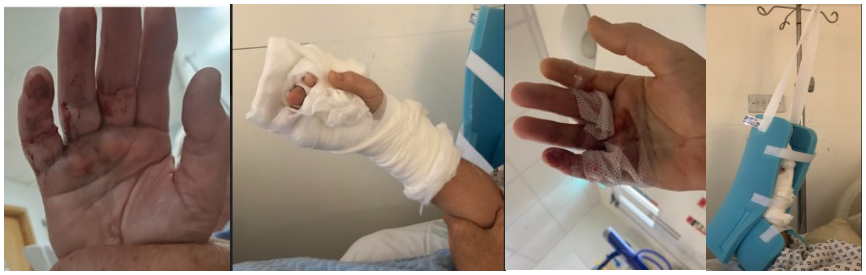

Figure 2: The patient's preoperative hands with bandaging and immobilization.

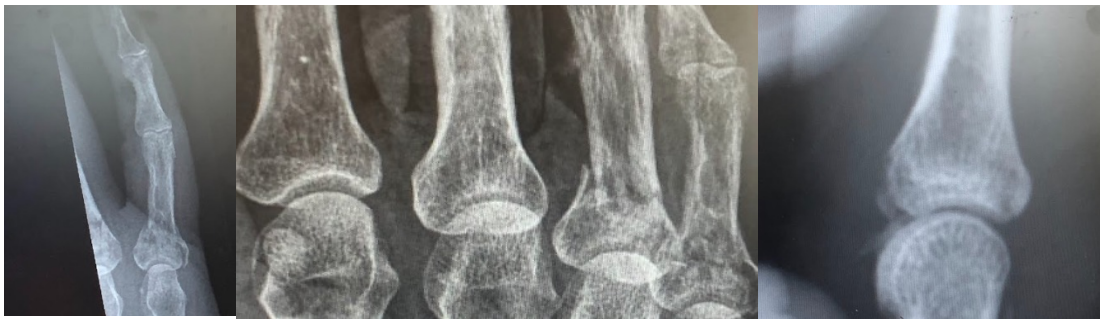

Figure 3: The displaced fractures in her ring and little fingers (left and middle pictures). Surprisingly, there were no fractures in the middle finger despite the open dislocation of the PIP joint (right picture).

patient had 0-5 degrees active flexion in 3rd-5th PIP joints and 0-80 degrees flexion in all 5 distal interphalangeal (DIP) joints. Passive range of motion was not examined due to pain. Sensations in all fingers were intact. The remainder of the examination was unremarkable.

Anesthesia

During this case, the handheld Butterfly iQ+ Ultrasound was instrumental for the precise application of the brachial plexus nerve block. This ultrasound, notable for its portability and compatibility with iOS devices, was crucial for identifying anatomical structures. Its utilization by Dr. Brian O'Donnell showcased not only its utility in navigating complex anatomy but also emphasized Butterfly iQ+'s advantages over traditional ultrasound machines. Key benefits include its affordability, user-friendly interface, and the ability to perform a wide range of scans without the need for multiple probes. The Butterfly iQ+ is distinguished by its innovative single-probe solution, utilizing advanced semiconductor technology to generate images for various applications—from cardiac and abdominal to musculoskeletal scans. This adaptability, combined with cloud-based storage and AI-driven image analysis, enhances clinical workflows and decision-making. Furthermore, its compact design facilitates bedside use, making it an invaluable tool in both emergency settings and routine care. This case underscores the Butterfly iQ+'s role in advancing point-of-care diagnostics, providing an effective educational tool while ensuring patient comfort during procedures[11,12].

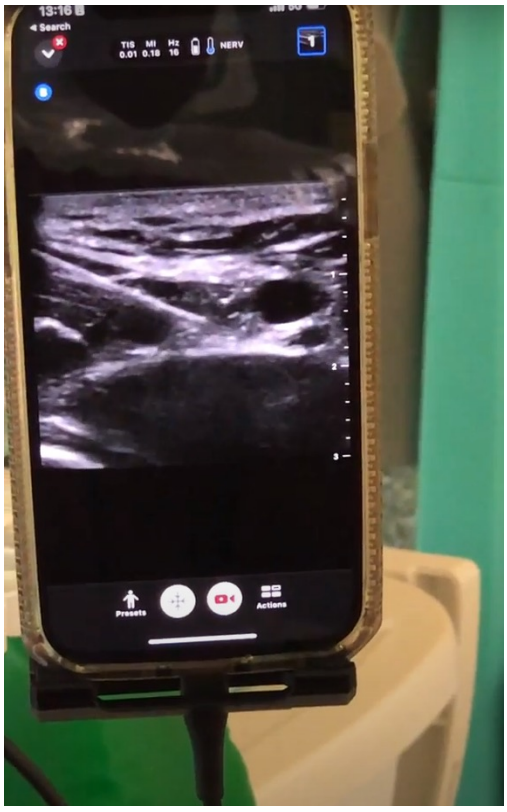

Figure 4: Dr. Brian O'Donnell taught the anatomical landmarks for the brachial plexus block using butterfly ultrasound and placing the needle adjacent to the median nerve complex to inject local anesthesia.

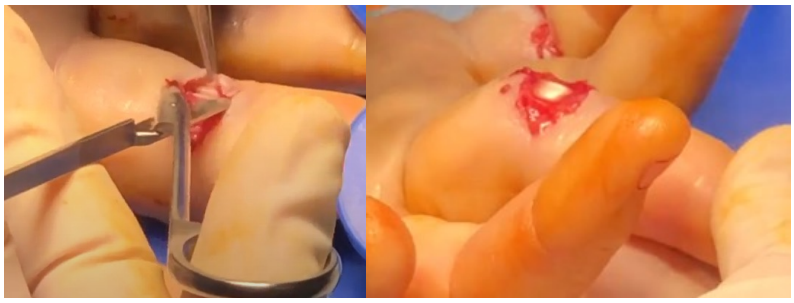

Figure 5: Middle PIP was explored, revealing that the nerves and blood vessels were intact but hyperextension is achieved because of volar plate damage.

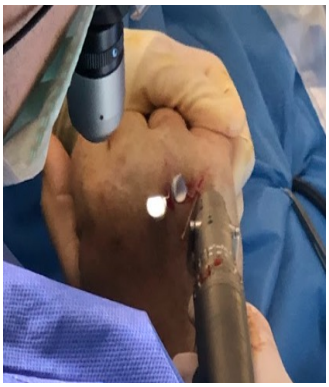

Figure 6: Installing the last pin in the 5th proximal phalanx.

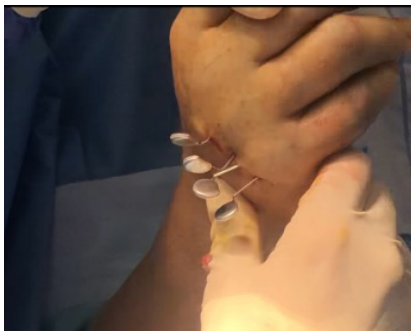

Figure 7: All four pins installed to fixate 4th and 5th proximal phalanx fractures.

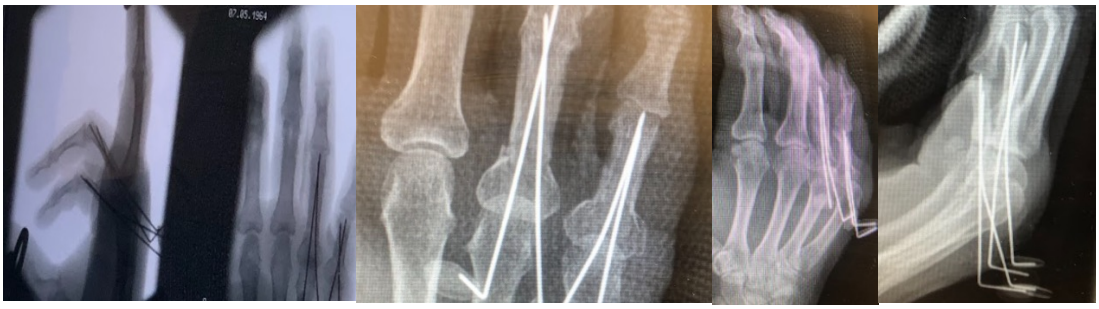

Figure 8: Two wires are installed in each phalanx to prevent rotation around the fracture, while simultaneously aligning and stabilizing the fracture.

Management

The patient was instructed to present back to the clinic for rebandaging every three days for the first week. She was prescribed paracetamol, ibuprofen, and Oxynorm 5mg every 4 hours for one week for pain management upon discharge. However, five days post-surgery, the patient reported experiencing severe pain, rating it at 10 out of 10. She described a sensation of feeling the wires in her fingers and had exhausted her prescription. Consequently, she sought an additional prescription from her General Practitioner for Oxycodone 5mg to be taken orally twice daily for a week.

By the second week, a new splint was tailor made to allow for DIP flexion for the 4th and 5th fingers as well as a dorsal splint to keep the middle PIP joint from hyperextending. The patient was instructed to check up each week for 4 weeks, planning to remove the wires 4 weeks after the operation.

The patient was initially planned to begin practicing piano again by week 6, but this was postponed until

Figure 9: This patient's post-operative care involved the use of a splint at a Position of Safe Immobilization or POSI splint, where the patient's 4th and 5th Metacarpal-Phalangeal joints were ideally kept at 40 degrees flexion, however, this patient was only able to achieve 30 degrees flexion secondary to 10/10 pain.

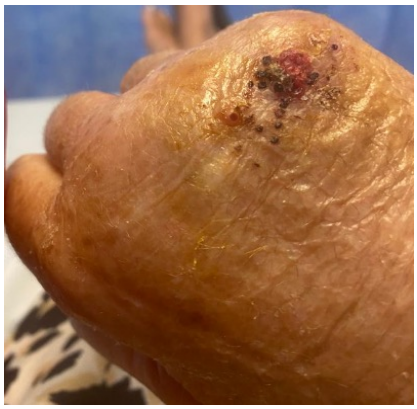

Figure 10: The patient's wire removal was postponed until week 5 to ensure maximal chance of stabilizing the proximal phalanges.

week 8 secondary to pain and stiffness.

Discussion

Challenges in this case were not insubstantial. Notably, the post-operative rehabilitation duration had to be recalibrated. The initial ambitious rehabilitation plan was tempered by the patient's level of pain, necessitating a more conservative approach. This emphasized the need for flexible management strategies, tailored to individual patient needs and responses. However, the importance of a patient's motivation, compliance, and active participation in occupational therapies could not be overstated.

Furthermore, the patient's search for solutions to their unresolved pain revealed possible discrepancies in pain management and anesthetic care. The prescription of Oxycontin, a potent opioid, directly contradicted the "Guidance for Opioid Prescribing for Acute Non-Cancer Pain, Post Operative Pain, and Post-Procedure Pain"[10]. This discrepancy raises concerns about the consistency of integration between tertiary and primary care. Namely, the oversight in the adherence to established pain management protocols where non-opioid alternatives and multi-modal pain management strategies might have been more appropriate. This case illustrates the need for a more cohesive approach to pain management that spans the continuum of care from acute hospital settings to community-based rehabilitation and primary care. Enhancing communication and coordination between healthcare providers across these settings is crucial to ensure that pain management practices are consistent, evidence-based, and aligned with best practice guidelines.

Conclusion

This paper demonstrated the Butterfly Ultrasound's role in clinical settings for anesthetic guidance and teaching, particularly in the administration of brachial plexus nerve blocks. The study also focused on restoring high-level hand functionality in a patient who played the piano, combining traditional techniques like temporary wires with the patient's motivation and therapy compliance. Challenges included adjusting post-operative rehabilitation plans to manage pain, underscoring the need for flexible, patient-centered strategies, and addressing the concerning rise of opioid prescriptions in Ireland.

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A Biopsychosocial Approach to 6-Year-Old Patient With Impetiginized Atopic Dermatitis: A Case Report

ANTHONY J. GOODINGS

Abstract

INTRODUCTION: This case report examines a 6-year-old male patient, with a complex presentation of impetiginized atopic dermatitis. The report adopts a biopsychosocial approach, considering the interplay of biological, psychological, and social factors influencing the patient's condition and management.

METHODS: The case study methodology involved a comprehensive review of the patient's medical history, family background, and current clinical presentation. A multidisciplinary approach was employed, integrating insights from dermatology, pediatrics, psychology, and social work to holistically address the patient's needs. Consent was obtained prior to drafting the case report.

RESULTS: Biologically, the patient's condition was characterized by severe exacerbation of atopic dermatitis, likely triggered by environmental pathogens, and compounded by iron-deficiency anemia. Psychologically, the severity of his skin condition led to increased irritability and social withdrawal, a notable deviation from his previously cheerful temperament. Social considerations highlighted the supportive family environment and the challenges posed by the visible nature of his skin lesions, affecting his school attendance and potential social stigma.

DISCUSSION: The case underscores the intricate relationship between biological predispositions, psychological resilience, and social environmental factors in managing pediatric atopic dermatitis. It highlights the importance of a multidisciplinary approach in treating such complex cases, considering not only the physical but also the emotional and social wellbeing of the patient.

CONCLUSION: This patient's case demonstrates the critical need for an integrated biopsychosocial approach in pediatric dermatology, particularly in complex cases like impetiginized atopic dermatitis. Tailoring treatment to address the multifaceted aspects of the patient's condition can lead to more effective management and improved quality of life for both the patient and their family.

Introduction

The International Classification of Functioning, Disability and Health (ICF) is a robust approach to a biopsychosocial model "in which health and disability are viewed as the result of the interaction between a health condition and contextual factors," including both psychological and social factors[1]. The late 1970s saw Dr. Engel's advocation and defence for the shift from a biomedical model of medicine to a biopsychosocial model. This movement was predicated on the assumption that the approach of doctors to a patient is derived from their instructed framework that serves to organize their knowledge[2]. The biopsychosocial model is now a well-established approach to the practice of medicine that enables members of a multidisciplinary team to address all the biopsychosocial determinants of health on an individually tailored basis[3].

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The nature of atopic dermatitis makes it particularly suitable for the application of the biopsychosocial model. This is because the condition leads to visible changes on the skin. These changes can evidently be detrimental to the patient's confidence and negatively affect social interaction. These social factors can contribute, over a period of time, to psychologic impacts on the child, such as a shy temperament and social withdrawal. So, while the condition indeed has a biomedical stem, there are numerous branches of the patient as a whole which are affected.

Case Background

The patient is a 6-year-old Irish-Caucasian male with a complex presentation to the inpatient pediatric service.

BIOLOGICALLY, the patient is experiencing a severe exacerbation of atopic dermatitis, now complicated by impetiginization. This acute episode is influenced by a combination of environmental, immunological, and psychosocial factors.

PSYCHOLOGICALLY, the severity of the patient's skin condition has shifted his demeanor from cheerful and engaging to increased irritability and social withdrawal, further exacerbated by sleep disturbances from itching and pain.

SOCIALLY, the patient's family, though proactive in allergen control and supportive of his needs, is facing emotional strain due to his condition. This has affected the patient's school attendance and raised concerns about the potential social stigma associated with his visible skin lesions

Case Details

PRESENTING COMPLAINT:

The patient, a 6-year-old male, is experiencing a severe exacerbation of atopic dermatitis with intense pruritus and discomfort, impacting his daily life and sleep.

FAMILY HISTORY:

The patient has a strong family history of atopic conditions: asthma in his mother and atopic dermatitis in his father, indicating a genetic predisposition. Recent exposures to infectious agents like respiratory syncytial virus (RSV) and Streptococcus Group A have exacerbated his condition.

PAST MEDICAL/SURGICAL HISTORY:

The patient's medical history includes allergic rhinitis and atopic dermatitis, along with iron-deficiency anemia, but no significant surgical history.

PREMORBID BEHAVIOR:

Prior to his current condition's exacerbation, the patient was cheerful, engaging, and resilient, actively participating in social interactions.

ENVIORNMENTAL AND SOCIAL FACTORS:

The patient's supportive family minimizes allergen exposure, yet the exacerbation of his dermatitis has disrupted family life and affected his school attendance, raising concerns about social stigma.

CURRENT MANAGEMENT:

The patient's treatment regimen includes topical therapies, antihistamines, and iron supplements, with a multidisciplinary team addressing his physical and psychological needs.

Clinical Findings

PHYSICAL EXAMINATION:

Physical examination revealed multiple vesicular, weeping, and crusting lesions predominantly located on his arms, legs, and trunk. The lesions were consistent with impetiginized atopic dermatitis. There were no systemic signs of severe infection such as fever or lethargy. His skin showed signs of chronic changes associated with atopic dermatitis, including lichenification and xerosis. The areas around the lesions were erythematous and edematous, indicating inflammation.

LABORATORY FINDINGS:

Routine blood tests revealed mild iron-deficiency anemia, which aligns with his past medical history. A swab of the skin lesions was taken for bacterial culture, which is critical in differentiating impetiginized atopic dermatitis from primary bacterial infections.

Discussion

BIOLOGICAL CONSIDERATIONS:

The patient's biological predisposition to atopic conditions is evident. His recent history suggests

that exposure to infectious agents, particularly from his sister's RSV and possible school-based exposure to Streptococcus Group A, may have served as precipitating factors for the current skin infection[4]. This is compounded by the history of iron-deficiency anemia, which could contribute to his overall vulnerability to infection and poor healing[5]. Iron-deficiency anemia has been associated with atopic dermatitis, however the mechanism for this is still unclear[6]. The physical examination supports the diagnosis of impetiginized atopic dermatitis, given the presence of vesicular, weeping, and crusting eruptions, without systemic signs of severe infection.

PSYCHOLOGICAL CONSIDERATIONS:

Psychologically, the patient's case presents a notable contrast between his typical behaviour and the impact of his dermatological condition. The severity and chronic nature of his atopic dermatitis have precipitated significant behavioral changes, reflecting the profound psychological impact of his condition.

The patient's increased irritability can be seen as a direct response to the constant discomfort he experiences. The pruritus and pain associated with his skin lesions are not only physical irritants but also psychological stressors. They disrupt his comfort and render him less tolerant of minor frustrations.

The social withdrawal observed in the patient is also a critical psychological aspect. Social interactions during childhood are essential for development, including language, emotional regulation, and relationship formation. The visibility of his skin condition, coupled with the discomfort it causes, may precipitate insecurity, and decrease engagement in social activities, leading to feelings of isolation.

Additionally, sleep disturbances increase his psychological distress. Chronic sleep deprivation is known to affect mood, cognitive function, and overall quality of life[7]. For the patient, the disruption of sleep likely contributes to his irritability and behavioral changes. It is also common for parent's own interpersonal relationships to be affected by the need to care for the child at night.

Similarly, chronic disease can lead to a sense of helplessness or frustration. This can degrade family dynamics, as parents or siblings may feel overwhelmed or unequipped to handle the fluctuations in the patient's mood and behavior[8].

SOCIAL CONSIDERATIONS:

The social context is composed of the supportive role of his family, the disruption caused by his illness, and the social implications of visible skin lesions. The patient's family provides a nurturing environment, proactive in managing his health needs. This active involvement reflects their understanding and commitment to his well-being, essential for the management of chronic conditions like atopic dermatitis[9].

The admission has significantly disrupted the family's routine and emotions. Managing a child with a chronic, visibly distressing skin condition can be emotionally taxing for caregivers. They may experience feelings of helplessness, frustration, or guilt, particularly when interventions do not yield immediate results[10]. This can cause a cycle of stress and anxiety that can further impact the patient's condition.

Social interactions are also impacted, particularly in school. His hospitalization led to absences from school, impacting his educational progress and social development. School-age children are acutely aware of peer perceptions, and visible skin lesions can make a child such as the patient vulnerable to social stigma or bullying, potentially leading to a decline in self-esteem and further social withdrawal[11,12]. This can lead to a reluctance to participate in group activities or physical education classes, further isolating him from his peers.

Conclusion

The case's psychosocial complexity highlights the necessity of a holistic approach, emphasizing that treating psychological aspects is as vital as addressing physical symptoms. A multidisciplinary strategy, encompassing family support, school involvement, and counseling services, is essential to manage the psychological and social impacts of the patient's condition effectively[13].

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Table 1: This table summarizes the principal points discussed in the three core domains of a biopsychosocial approach.

Factor Type	Biological	Psychological	Social
Predisposing	• Strong family history of atopy • School-aged child regularly • exposed to pathogens • Dislike and poor adherence for emollients.	• Shy temperament makes the patient more vulnerable to stress.	• Social interactions and self-esteem can be impacted by the visible skin lesions.
Precipitating	• Sick contact (RSV) from sister • Sick contact at school (Gr. A Strep) • Recent VZV infection	• Recent stressors such as his sister's illness disrupting the household routine.	• Stress of a new social environment and interactions can precipitate or worsen exacerbations.
Perpetuating	• Initial refusal of antibiotics (PO) • Poor adherence to emollients causing continued skin breakage and infection.	• Sleep disturbances from intense pruritis and other symptoms can cause chronic distress and psychological disturbances	• Absence from school can disrupt the patient's routine and lead to worry about missing out, this can perpetuate stress and his illness.
Protecting	• Otherwise good physical health • Administration of IV antibiotics.	• The patient has demon-strated previous resilience in adapting to different sit-uations such as beginning school.	• Patient has an extremely supportive fam-ily network to help support him with feeling better, catching up with school, and help him cope to mitigate distress. Parents able to take time off work to stay with him in the hospital

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Post-Partum Psychosis – A Case Report

FELICIA DEONARINE

Abstract

The patient (NS) is a 5 month post-partum 32 year old woman, G2P2, who presented to the Cork University Hospital (CUH) Emergency Department by ambulance. She presented to the ED distressed, anxious and confused. Her family history is significant for depression. Her personal history is significant for long periods of separation from her spouse and an increased workload and chores list at home, leading to high levels of stress and anxiety. Her past medical history includes two births, both caesarean and non-complicated. However, she contracted a SARS-CoV-2 infection prior to her most recent delivery. Her eldest child is 6 years old and her most recent is 5 months. Prior to NS's deterioration, she was described as level-headed, dependable, quiet, and overall an extremely competent mother. Her physical examination was non-contributory. Finally, on December 5th 2022, her condition improved. Her MSE showed a tidy appearance, non-paranoid body language, sequential speech, reactive mood, logical and non-paranoid thoughts, good insight about psychosis, excellent cognition, and low risk for harm to herself or others. In this case report, the biopsychosocial aspects of the patient's recovery are discussed.

Case Background

NS is a 32 year old married immigrant from an African country. She is a stay-at-home mother who arrived by ambulance from a grocery nearby, where she had called the gardai to report that she was being followed. She reported feeling that she and her children were unsafe. The examination and a collateral history with the patient's spouse revealed that over the last week she was becoming more paranoid about the safety of herself and her children and believed that her husband was poisoning their children's meals.

Psychiatric assessment in the ED revealed heightened emotions, persecution delusions, paranoia, distress, and anxiety. NS was also very confused as she didn't recognize doctors she had seen previously and kept asking for them to show her their identification. She calmed within hours and accepted a sandwich and water, but refused to eat anything unless it was given to her in a sealed package. On November 28th 2022, the patient awoke at 7:30 AM and asked to leave. The medical team tried to calm her but she became agitated and security needed to be called. She refused to have her vitals checked, rejected all food and water, and she self-removed her cannula. The patient was subsequently involuntarily admitted to St. Stephen's Psychiatric Hospital in North Cork on November 28th 2022 for inpatient care.

Upon admission to St. Stephen's, the patient reported difficulties sleeping for four nights prior to admission. She also reported unintentional weight loss and muscle weakness. NS denied thoughts of self-harm and suicide. She also did not believe that her thoughts or actions were being controlled by others. Memory was impaired as patient reported feeling very forgetful. Concentration was also impacted as patient reported difficulty with focus. At this time, all the patient wanted was to return to her children so that she could protect them as she sensed danger.

According to the collateral history, NS's spouse noticed a change in the patient's personality one week prior to admission to the ED. She was acting very confused, holding the children too tightly and was acting very aggressively toward family members. The two days prior to admission, she would not let her spouse feed the children because she was worried he was poisoning the baby food. He also reported that NS hadn't slept in the four nights prior to admission and instead spent her time in bed staring at her mobile device. Her spouse stated that normally "she is very stable and is a brilliant mother".

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On December 5th 2022, the patient was interviewed. At this time, she reported no difficulties with sleep and had been obtaining seven to eight hours per night in the previous three days. She also reported no issues with her appetite, memory, concentration or muscle strength. NS denied thoughts of self-harm and suicide, and a belief that her thoughts and actions were being controlled by an external force. At this time, the patient did not stress a deep desire to return home to her children and wanted to do her part to help herself heal. According to the patient, the stressors that made her feel paranoid and anxious, which lead to a lack of sleep, included the combination of the recent birth of her second child five months prior (increasing the workload at home), covid concerns, noticeable changes in her spouse's personality, her spouse's previous family (ex-wife and three children) becoming too involved in her marriage and family life, and concerns about "new strangers in the country".

Her family history is significant for depression. Her mother was diagnosed with depression years ago and is currently managed with medications. The patient reports her mother's personality to be emotionally unstable and her relationship with her father to be difficult with little communication. The patient's 20 year old brother was recently diagnosed as bipolar managed with medications.

NS's 52 year old husband is healthy physically, employed in a work plant and works abroad. According to the patient, he has become more grumpy recently.

The atmosphere at home while growing up was not always warm. Her parents sometimes argued because her father often became belligerent after drinking alcohol. NS would not admit to any physical abuse, neglect, or trauma during childhood. The family had low income, and they often struggled with finances. Despite the difficulties in her parent's relationship, they remained married and the patient remained close to her mother.

NS has no past psychiatric history or previous episodes of self-harm or suicidal ideation. Medications that were administered in the hospital that have been discontinued since include Alprazolam, Paracetamol, Midazolam, and Lorazepam. At the time of history taking, NS was taking olanzapine at night.

On general inspection, the patient was reactive and well-dressed in a white shirt and black pants. All physical examinations were normal. A urinalysis did not reveal any abnormalities.

Discussion

NS presented with persecution delusions approximately 5 months after giving birth to her second child. The likely diagnosis is postpartum psychosis (PPP) due to the temporal proximity to child birth. However, there are some potential diagnoses that must be considered as this is the patient's first psychotic episode. The differential diagnoses in order of likelihood include a first presentation of schizophrenia, bipolar 1 relapse with paranoia, and organic causes of psychosis. The differential diagnoses can be excluded based on the history and laboratory findings. The diagnosis along with the aetiological factors, specifically the perpetuating and protective categories, are used to formulate a care plan for the patient. The most significant perpetuating factors include the patient's relationship with her spouse and his first family, and her cultural isolation. She was separated from the cultural influences of her African society leading to limited exposure to Irish customs, traditions, lifestyles and languages. To reduce the impact of these factors on the life of the patient, psychological and social management is important, which includes the home based crisis team and counselling services. Unlike the perpetuating factors, the protective factors must be strengthened for a better prognosis. These include beneficial social connections, medications to treat the persecution delusions, and monitoring by the psychiatric team for relapse. The patient's prognosis is excellent as treatment was initiated early. In addition, a good prognosis is more likely if the care plan is followed. However, there is an increased likelihood of recurrence in subsequent pregnancies.

Globally, PPP is a very rare form of postnatal depression, but it has serious risks and complications including maternal death[7]. It is characterized by confusion, intrusive thoughts, hallucinations, delusions often involving the children, and paranoia[1]. NS developed symptoms five months post-partum, but most cases occur immediately, within days to the first six weeks after birth. The condition is often misdiagnosed, mismanaged, or missed entirely by both obstetricians and psychiatrists due to stigma, lack of knowledge and difficulty in recognition of symptoms[8]. This led me to consider the risk factors that exist for PPP and what methods can be used to determine the correct diagnosis.

As PPP is very rare, it would be important to identify pregnant populations that are increasingly susceptible to development of this condition. Some of the known risk factors for postpartum psychosis include personal or family history of bipolar disorder, prior episode of PPP, and sleep disturbances[8]. According to the literature, personal history of bipolar disorder is the strongest risk factor for developing PPP[9]. However, a retrospective cohort study of 116 women who experienced episodes of mania or depression with psychotic features at least six weeks postpartum showed only 33% had a previous psychotic episode and of these only 1/3 were previously diagnosed with bipolar disorder[10]. NS is likely to be similar to the 66% of patients in this study that did not have a previous psychotic episode and did not have a history of bipolar disorder.

The relevance of family history to the development of PPP might be related to genes. Studies have shown that an MTHFR C677T variant influences folate metabolism and could be implicated in both postpartum depression and PPP[11]. More research is required to completely uncover and identify the genes that impact the development of PPP. NS's family history is significant for depression with her mother, and bipolar disorder with her brother. She has a strong family history for risk factors associated with PPP.

Sleep loss is a common occurrence in the postpartum period due to significant changes in the new mother's lifestyle and daily routine. A cross-sectional study on women with bipolar disorder showed that women who had previously experienced manic episodes due to sleep loss were twice as likely to experience an episode of PPP in the future (OR = 2.09, 95% CI = 1.47-2.97, $p < 0.001$) compared to women who did not report sleep loss and manic episodes[12]. Interestingly, this association was not discovered for postpartum depression ($p = 0.526$). NS reported sleep disturbance was a significant precipitating factor for her condition. The importance of good sleep hygiene especially in the postpartum period should be highly stressed during visits to medical professionals.

There has been some research into two potential risk factors for PPP including pre-eclampsia and primiparity. One Danish cohort study including 400,717 primiparous women with a singleton delivery between 1995 and 2011 demonstrated a higher risk for first-onset psychiatric episodes during the first month in the postpartum period for these women [IRR 2.93, 95% confidence interval (CI) 2.53-3.40][13]. In addition, pre-eclampsia increased this risk (IRR 4.21, 95% CI 2.89-6.13). Furthermore, women who had both pre-eclampsia and a somatic co-morbidity had the highest risk of psychiatric episodes during the first three months of the postpartum period (IRR 4.81, 95% CI 2.72-8.50). Pre-eclampsia and primiparity were not relevant to NS's current history, but they are worth considering as reminders that additional risk factors are still being discovered.

After acknowledging the existence of specific risk factors, the correct diagnosis can be ascertained using screening tools and additional psychosis-related questions. According to a publication in 2018, there is no screening for antenatal depression in Ireland and there is no data indicating the prevalence rates of depression for patients admitted to Irish obstetric services[14]. Post-partum depression can be screened for during the first visit after birth, both formally with a screening tool such as the Edinburgh Postnatal Depression Scale (EPDS) or informally with questions directed towards the patient regarding their mood and overall mental health. The EPDS was originally developed in the United Kingdom and is now used globally in several countries to screen for symptoms of maternal depression by assessing emotional experiences of the patient over the past seven days using ten Likert-scale items[15]. The original validation study showed 9 out of 10 post-partum women who were diagnosed with depression by a psychiatrist were correctly identified by the EPDS in a blinded comparison. The EPDS does not specifically address psychotic symptoms, thus it would be important to include questions during history taking from the patient and family such as: (1) Is this the patient's first psychiatric presentation; (2) Does she have a history of depression, mania or both?; (3) Is there family history of bipolar disorder; (4) Does the patient use any drugs; and (5) Have there been any thoughts of harming herself or the child? In summary, acknowledgement of the various risk factors associated with PPP, and consideration of EPDS and screening question results might be useful to aid in the correct diagnosis of PPP during routine post-partum appointments.

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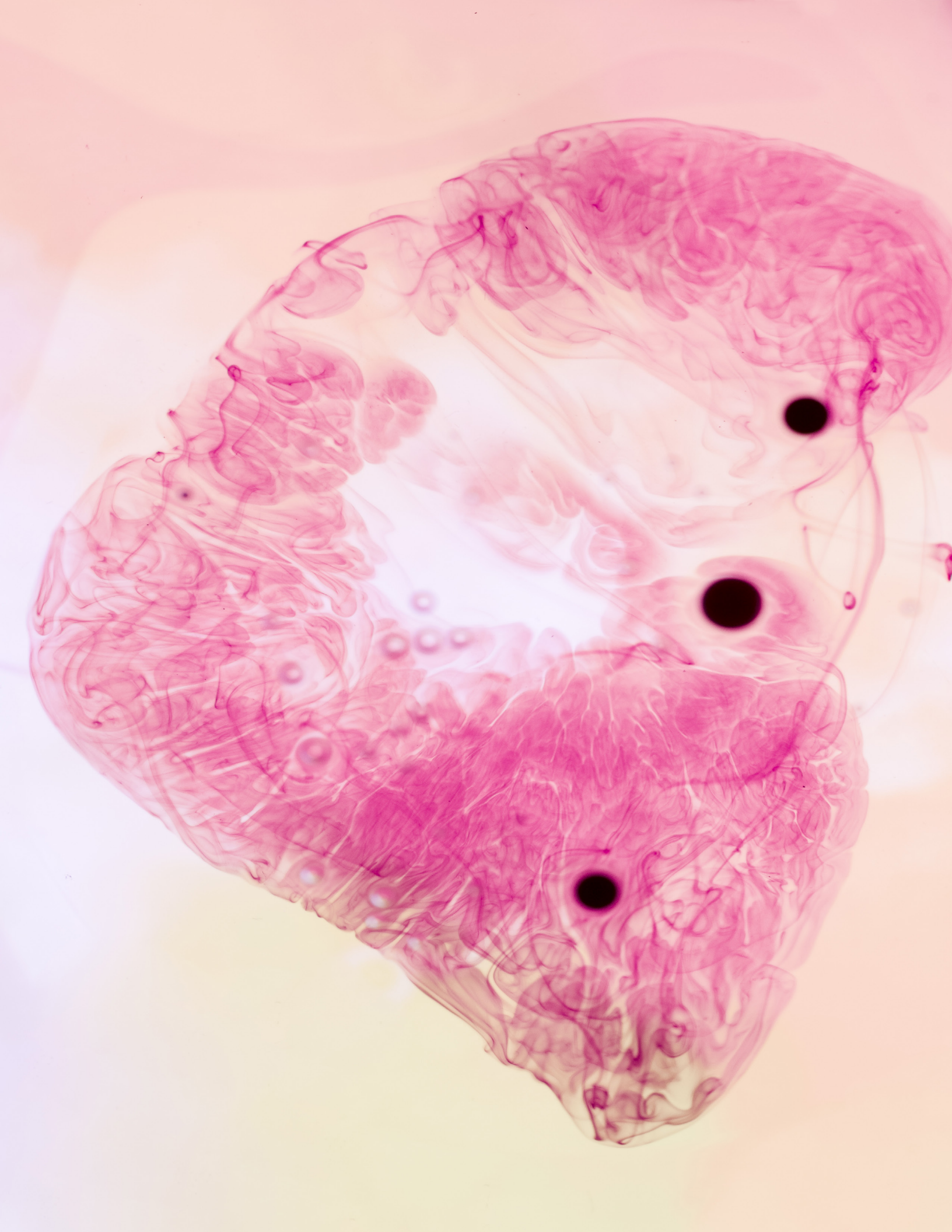

HELLP Syndrome – A Biopsychosocial Case Report

FELICIA DEONARINE

Abstract

This case concerns a 30 year old female patient (SB), G2P1 (2 gravidity, 1 parity), who was admitted to the high dependency unit at Cork University Maternity Hospital in Cork, Ireland at 37 weeks and 1 days' gestation. She was admitted after experiencing a 5 minute tonic-clonic seizure at home with no obvious relieving factors. Relevant positive symptoms included nausea, headache, and right hypochondrial pain. Relevant negative symptoms included denying tongue biting, incontinence, speech or visual disturbances, sensory or mental aura, vomiting, and cyanosis. There were no drugs, trauma, recent illness, or history of previous seizures. On examination, SB was confused and displayed signs consistent with pregnancy. In addition, a focused examination revealed hypertension, hyperreflexia, right hypochondrial pain, and lower limb oedema. The investigations included a urine dipstick, CT scan, and blood tests which showed anaemia, low platelets and proteinuria. The history, examination, and investigations in this case were consistent with a presentation of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome. In this case report, the biopsychosocial aspects of the patient's recovery are discussed.

Case Background

While at home, the patient (SB) experienced a 5 minute tonic-clonic seizure causing a fall on her right side with a 5 minute recovery time. Her spouse called the ambulance after placing SB into the left lateral decubitus (LLD) position. SB lost consciousness and remembers waking, but feeling confused.

With regards to obstetric history, SB experienced a natural miscarriage at 5 weeks gestation in 2017. She also delivered a 1.77 kg male baby in 2018 by an emergency caesarean section (CS) at 34 weeks due to intrauterine growth restriction. Her baby required transfer to the neonatal intensive care unit for half hour of continuous positive airway pressure and was discharged on day 11 due to poor feeding.

Her current pregnancy was planned with an estimated delivery date of November 18th 2022. At her last antenatal visit, her blood pressure was normal and she did not have proteinuria. However, foetal biometry showed a growth delay of 4 to 5 weeks with an estimated weight of 2056 grams and amniotic fluid index of 7 cm. The patient's blood type was group B rhesus positive and the blood results did not show an active infection. The patient also possessed immunity against HBV, rubella, and varicella. Foetal movements had been felt since 17 weeks and the oral glucose challenge test was normal.

The patient's gynaecological and past medical history was insignificant. The patient's medications included aspirin due to intrauterine growth restriction in her previous pregnancy, and folic acid. She had no known drug allergies. In addition, she was vaccinated against tetanus, diphtheria, pertussis, coronavirus, and influenza during this pregnancy.

The patient's family included a 60 year old father with stable angina and type 2 diabetes, and a 58 year old mother who had no complications in her two previous pregnancies. Both her 25 year old sister and her 4 year old son are alive and well. She had no known family history of neurological, cardiac, obstetric, or gynaecological conditions.

The patient lives with her spouse of 8 years and her son in a two story home about 20 minutes from the hospital. She has been a hairdresser for 5 years and her spouse is a nurse in psychiatry. Her son attends a

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local pre-school. The family is financially stable and non-religious. The patient has several family members living either walking or driving distance from her home who can provide support if necessary.

SB does not consume alcohol or use recreational drugs. She takes 30 minute walks 3-4 times per week and swims once per week. Her diet is healthy with a variety of fruit and vegetables and includes decaffeinated tea and small amounts of chocolate, but no coffee. SB started smoking tobacco at 18 years of age. She stopped smoking prior to her previous pregnancy and restarted for 6 months after the delivery. Finally, SB stopped smoking tobacco again at age 29 prior to her current pregnancy.

On general inspection, the patient was lying uncomfortably with a distended abdomen consistent with gravid uterus. Upon closer inspection, linea nigra, several striae gravidarum and an everted umbilicus were apparent on the abdomen. The symphysio-fundal height was 37 cm, consistent with the pregnancy gestation. Bedside ultrasound showed a longitudinal lie with cephalic presentation. The patient's blood pressure was 160 systolic and 89 diastolic. Cardiotocography showed periodic decelerations with recovery to baseline foetal heart rate of 160, with some accelerations and moderate variability. The neurological examination revealed confusion with a Glasgow Coma Scale score of 14 out of 15 and hyperreflexia of the lower limbs. The abdominal examination revealed right hypochondrial pain and an absence of ascites. The cardiovascular examination revealed bilateral lower limb oedema. All other examinations were normal.

Discussion

SUMMARY:

The biopsychosocial model is a framework developed by George Engel in 1977 which is used clinically, during guideline development and by the World Health Organisation's International Classification of Functioning[1]. The Biopsychosocial model examines the interconnection between biological, psychological, and social aspects of health and disease. Consideration of all three factors allows health care professionals to tailor a care plan and alter the methods used to approach patients with difficult decisions[2].

BIOLOGICAL:

The symptoms experienced by SB including hypertension, seizure activity, increased intracranial pressure (a headache), and right upper quadrant abdominal pain, was consistent with a presentation of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (HS)[3]. This condition occurs on the background of pre-eclampsia which is defined as new onset hypertension with a systolic blood pressure (BP) of over 140 or diastolic BP over 90 after 20 weeks' gestation, with the presence of proteinuria[4]. SB was officially diagnosed with HS upon further examination and the completion of additional investigations including a full blood count, liver enzyme panel, liver function tests, and urine analysis. HS is characterized by haemolysis (H), elevated liver enzymes (EL), low platelets (LP), and proteinuria[3]. The patient's blood and urine results were 11.2 g/dL for haemoglobin (reference range: 12.1 to 15.1 g/dL), 69 000 platelets per microliter (reference range: 150,000 to 450,000) and 4+ for proteinuria. This syndrome occurs in approximately 0.5-0.9% of all pregnancies and 10-20% of all pre-eclamptic cases[5].

HS is associated with maternal complications including placental abruption, disseminated intravascular coagulation, hepatic hematomas and rupture, and acute kidney injury[6]. It is also associated with neonatal complications including prematurity, respiratory distress syndrome, and small for gestational age. Regardless of the aetiology, sustained seizures can lead to a significant decrease in oxygen. Therefore, seizures pose a substantial risk to both the life of the woman and her unborn foetus.

HS and post-ictal management first begins with stabilization of the woman[7]. In general, if the syndrome occurs after 34 weeks' gestation, immediate delivery is the first choice of management[5]. As SB was at approximately 37 weeks' gestation, the case management consisted of immediate delivery after stabilization. To reduce the patient's BP, SB was given 10 ml of labetalol at 5mg/mL through an intravenous (IV) line. Labetalol, along with nifedipine and methyldopa, are safe and effective drugs that are often used in acute cases of maternal hypertension[8]. Magnesium sulphate, an anti-seizure prophylaxis medication, was also administered to SB through an IV line at 1 g/hour[9].

Unfortunately, SB suffered from another five minute tonic-clonic seizure while in the triage unit. SB was promptly rolled onto the LLD position and provided with an oxygen mask. Cardiotocography monitoring showed foetal compromise with prolonged decelerations lasting approximately three to four minutes. The dosage of magnesium sulphate was increased to 2 g/hour and SB was immediately prepped for a CS as soon as the seizure subsided and her BP began decreasing.

After the emergency CS, 10 units of oxytocin and 250 micrograms of carboprost tromethamine were administered by IV due to an atonic uterus. These medications are standardly used to treat uterine atony, which poses a major risk for postpartum haemorrhage and maternal mortality[10]. The medications proved effective and there was no substantial haemorrhage. After the CS, SB was transferred to the intensive care unit and discharged after three days of careful surveillance and review due to an episode of postpartum hypertension (156/90 BP). On discharge, SB was provided with a prescription for nifedipine 10 mg PO twice daily, and a follow-up for repeat blood testing and BP check with her general practitioner (GP).

BIOLOGICAL:

HS results in a unique maternal experience stemming from a lack of control and knowledge. Five psychological themes can emerge in HS including (1) premonition of a bad event about to occur, (2) symptoms, (3) betrayal regarding healthcare providers and their own bodies, (4) whirlwind due to the speed at which events unfolded, and (5) loss of the initial joy of motherhood[11]. Emotions experienced can include fear, frustration, anger, and guilt. Therefore, it is important to display empathy, adequately communicate with the patient and the family, and explore the patient's main concerns as time progresses.

After every seizure, the medical personnel would speak with SB and provide her with all the information available regarding her condition. The professionals would communicate clearly, sit or kneel at eye level to the patient and ask if there were any questions at the end of the interaction. These tactics were all necessary to ensure the patient didn't feel anxious, which could lead to additional BP elevation and psychological trauma. SB's spouse was also quickly updated when he arrived.

Women experiencing HS can also develop post-traumatic stress disorder (PTSD)[12]. PTSD symptoms might include nightmares, flashbacks, numbing of responsiveness, hypervigilance, irritability, and difficulty concentrating. Therefore, patients should be followed by their GP for months after the delivery. SB was scheduled for a follow up appointment with her obstetrician during a post-natal appointment in approximately 2 months after the delivery. She would be managed by her GP afterwards.

SOCIAL:

The diagnosis of HS can pose great risks to the physical, mental and psychological aspects of the patient. Family and friends can be a great support to aid in the patient's recovery. A previous systematic review showed that low social support was associated with significant risks of depression, anxiety and self-harm during pregnancy[13]. In some cases, religion can be a support system for the patient[14]. HS was not religious, but had a large group of family and friends living in the area that were willing to offer their time and show their support.

SB's spouse was also very supportive and kind, which limited her feelings of fear and anxiety. SB's spouse expressed a plan to ensure care of his wife and child. He said he already informed their family and friends and had planned a meeting with them for when they arrived home.

The barriers to social support for SB were the precautions implemented due to the COVID-19 pandemic regarding restrictions for visiting hours and visitor numbers. Isolation in the hospital from social support can increase the risk of patient depression and anxiety[15]. Thankfully, SB stayed in the hospital for only a few days and was able to have the constant presence of her spouse. A cot was placed in the patient's room for her spouse. In addition, although their new baby girl was healthy with APGAR scores of 9 at 1 minute and 10 at 5 minutes, she was kept in the neonatal unit until SB was ready for discharge. This provided the parents with easy access to their baby and less stress in their lives with regards to finding neonatal care for the duration of SB's hospital stay. The patient's first child was being well taken care of by SB's parents who lived nearby. This provided additional relief for the patient and promoted psychological recovery.

Conclusion

This case report describes the journey of a pregnant woman through a hospital admission for a complication of pre-eclampsia known as HS. It includes the interconnected biological, psychological, and social aspects that were considered in the treatment and management of this patient. Previous research and knowledge about patient care was used to reduce the negative effects on this patient. This case report demonstrates the importance of tailoring a care plan to the patient based on the factors that would maintain a good prognosis and protect against a worsening condition.

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The Use of Artificial Intelligence in Clinical Diagnostics – Challenges To Consider For Implementation

PÁDRAIG CRONIN

Introduction

Whilst many technological advancements have revolutionised healthcare throughout the 21st century, one of the most significant is Artificial Intelligence (AI). AI is generally regarded as the capability to imitate intelligent human behaviour using machines, and is based on computer science, statistics, algorithms, machine learning, information retrieval, and data science[1]. AI has permeated into many domains of healthcare including Clinical Diagnostics. While AI chatbots (such as those used in Babylon and Ada) are being used by patients to identify symptoms and recommend further actions in community and primary care settings, more recent advances in the technology with larger datasets have provided users access to a more extensive array of clinical conditions[2].

However, as these tools are constantly being developed with an ever-increasing dataset of clinical cases, certain challenges threaten the implementation of an accurate and effective model. In this article, the issue of Data Bias, and Data Handling will be examined within the context of Clinical Diagnostics, and how these factors threaten the development of such AI Healthcare tools.

Data Bias - An Unrepresentative Algorithm

Data Biases are a fundamental threat to the development of AI Tools which arise from errors within the data collection process. These biases can produce harmful results for people, including social discrimination and a significant loss of trust from society, if they are not identified and mitigated[3]. This is particularly true for medical diagnostics where a wide range of signs, symptoms, laboratory results, and clinical presentations are used across variable age ranges, genders, and ethnic backgrounds to determine an accurate diagnosis.

One of the most important steps in the development of any AI Tool is the cultivation and development of a suitable dataset with which to train the model upon. This dataset will form the basis of the algorithm that will ultimately assign a diagnosis. When developing such a dataset, many variables must be examined in order to create a fair and balanced outcome. Errors in the collection of clinical data include, but are not limited to:

- Unrepresentative Case Distribution – Creating a skewed probability output which favours certain population cohorts, and thus misdiagnoses minorities within the population.
- Vague or Irrelevant Signs/Symptoms – Drawing correlations between symptoms and diagnoses which may not be linked, and can result in model confusion and/or reduced accuracy.
- Incorrect Signs/Symptoms Input – Generation of confusion within the model based on a mismatch between symptoms and diagnoses.
- Reuse of Clinical Cases – Potential to bias the model toward a particular diagnosis, overrepresenting a particular condition.

In the event of any of the above circumstances, the final AI algorithm may be unrepresentative of the actual patient cohort being diagnosed, and is liable to produce inaccurate or false diagnoses. To combat this internal bias, each source of error must be carefully examined when reviewing the dataset prior to model development, and the process repeated with the addition of new data throughout the iterative training process.

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Data Handling – Balancing Patient Privacy With Model Development

A major risk which poses a threat to the development of AI Clinical Diagnostic tools is the associated data handling during model development. A critical step in the development of any artificially intelligent model is the input of real data which can be used to drive accuracy and precision of the diagnostic outcome.

Many open-source AI tools collect the data which input by the user for two reasons: model development, and retesting of the model during iterative training. In order to carry this out within the context of a clinical diagnostic AI tool, patient data such as age range, ethnic background, signs/symptoms, and diagnosis would need to be accessible and stored for use. An example of this is the OpenAI tool, ChatGPT, which states in its guidelines that "Your conversations may be reviewed by our AI trainers to improve our systems"[4].

This presents with it the significant challenge of how to balance model development with patient privacy. Large scale data privacy laws which have been implemented within the past decade include the European Union's General Data Protection Regulation (GDPR) Article 17, which holds the "right to be forgotten" as a fundamental pillar[5]. This right entitles patients to have their data withdrawn from the databases which are being used for AI development. With this arises the conflict between developing an accurate model whilst accounting for patient privacy rights.

A possible solution to this would be the anonymisation and redaction of patient data which could then be used to drive model development. This process would fulfil the GDPR Article 17 requirements if a patient's identity cannot be recovered from the anonymised data[6]. This would require significant resources and procedures within the companies developing these AI tools. However such anonymisation would guarantee patient safety whilst preserving data that is critical for product development.

Conclusion

AI Toolkits are rapidly becoming an everyday feature of many disciplines, including healthcare. As demonstrated by its extensive use in other areas of industry, AI is an incredibly powerful tool that has the potential to transform healthcare in the future. However, it is not a perfect tool in its current form for a number of reasons as discussed above. Two areas of improvement include:

- Targeted and careful dataset design for algorithm development in order to mitigate diagnostic bias across various patient cohorts and disease profiles.
- Development of concrete and executable guidelines within the software training process which maintain patient privacy whilst also protecting model development.

Once both of these areas have been examined and addressed, AI not only has the potential to improve efficiency in the clinical environment, but also to improve patient diagnostics through the implementation of highly accurate clinical decisions driven by real world data.

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Psychedelic-Assisted Therapy: Magical Thinking or a Meaningful Treatment for Mental Illness

MEGHA KODANCHA

Abstract

Psychedelics are psychoactive substances that are known to alter perception, alter mood, and affect numerous cognitive processes. Throughout history, psychedelics were utilized in ceremonies and rituals, and in the 20th century, their utilization in psychiatry began. In the 1960s they became a banned substance and are only recently being revisited for their benefits. The main forms of psychedelic substances being studied today are Lysergic acid diethylamide (LSD) for addiction therapy, Psilocybin for palliative care, and 3,4-Methylenedioxymethamphetamine (MDMA) for post-traumatic stress disorder (PTSD). This paper focuses on the benefits of utilizing psychedelics for specific psychiatric conditions and is meant to encourage further research into this domain of Psychiatry.

Psychedelics used to be considered as this gateway to connect communities with nature, heal a troubled mind, or even "generate the god within" in some cases[1,2]. They have been utilized in various cultures throughout history for spiritual, medicinal, and religious reasons[1]. Praised in Indian Vedic hymns, incorporated in Greek ceremonies, and given during Mayan religious rituals - there are countless accounts of the usage of psychedelics throughout history[1,2]. Then, from 1960-2000, the perception of psychedelic drugs shifted - it became this extremely toxic substance associated with "scrambling" chromosomes, psychotic breaks, and suicide[2]. Despite initial clinical success, psychedelics were cast as illegal substances with no medicinal use due to their misuse by the public and the political climate at the time[1,3].

Psychedelics, otherwise known as serotonergic hallucinogens, are psychoactive substances that alter perception, alter mood, and affect numerous cognitive processes[1]. Psychedelics are agonists or partial agonists at brain serotonin 5-hydroxytryptamine 2A receptors, with particular importance on those expressed on apical dendrites of neocortical pyramidal cells in layer V of the brain cortex[1]. The main forms of psychedelics seen today are (a) Lysergic acid diethylamide (LSD), a chemically synthesized hallucinogen, developed from ergot, a kind of mold that grows on rye grains[1,2], (b) Dimethyltryptamine (DMT), a natural occurring psychedelic found in the bark and nuts of certain trees from Central and South America[1,2], (c) Mescaline, a naturally occurring psychedelic substance found in certain species of cactus[1,2], (d) Ololiuqui, a naturally occurring psychedelic that is found in the seeds of the morning glory flower[1,2], (e) Psilocybin, a psychedelic substance found in certain fungi, sometimes referred to as magic mushrooms[1,2], and (f) 3,4-Methylenedioxymethamphetamine (MDMA), a chemically synthesized stimulant with mild psychedelic properties that was originally synthesized as a bleeding-control medication[1,2].

Many of these psychedelics continue to be utilized as a part of spiritual practice and some have even been introduced into modern Western medicine[2]. The usage of psychedelics for medicinal use was initially halted in the 1960s after the 'War on Drugs' campaign deemed them as harmful substances illegal for ingestion[2,3]. However, this is a misclassification: unlike other illegal drugs, psychedelics are not addictive substances and can be utilized in therapy for certain psychiatric conditions[1]. The remainder of this paper focuses on the benefits of utilizing psychedelics for specific psychiatric conditions and is meant to encourage further research into this domain of psychiatric care. MDMA, Psilocybin, and LSD are the main psychedelics being researched today for having medical benefits in psychiatric patients[2,3].

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First synthesized in the early 20th century, MDMA may be one of the first psychedelic drugs to be relegalized for clinical usage[3,4]. MDMA's mechanism of action varies from its other psychedelic siblings as it does not target serotonin receptors, rather it works as an amphetamine and influences levels of dopamine and norepinephrine[1]. MDMA can take people to dark, avoidant memories and remove the fear and anger associated with those memories/feelings[3]. This makes it an ideal drug to use in post-traumatic stress disorder (PTSD) and phobias therapy[5]. The gold standard for treating fear-related disorders is extinction-based exposure therapy (ET), a therapy based on exposing the fears/triggers of a person in a safe environment to help them become acclimatized to them, but this is shown to be ineffective for up to 35% of subjects[5]. This prompted some psychiatrists to turn to psychedelics as an addition to ET[5,6,7,8]. By reducing activation in brain regions implicated in the expression of fear and anxiety-related behaviors (e.g., the amygdala), MDMA may allow for the reprocessing of traumatic memories and generate a healthier emotional engagement with therapeutic processes[6]. Many people who have described their experience with MDMA report that it improves their ability to revisit memories and develop an acceptance of their trauma[3]. Veterans who would demonstrate debilitating responses to aspects of daily life would use MDMA and would no longer find these aspects triggering[2]. The data from various studies do suggest that when used in safe clinical settings MDMA can help individuals combat their PTSD and phobias.

It is important to consider therapy as more than just a solution to illness/problem, but instead, as a method to improve the quality of one's life; this is extremely useful for end-of-life care in cancer patients[9]. Of all the psychedelic drugs, psilocybin is reported to have the most favorable safety profile and has been used in studies with cancer patients[9,10]. In 2019, Usona Institute received US Food and Drug Administration "breakthrough therapy" status for using psilocybin in major depressive disorder (MDD), and since then its usage alongside chronic conditions has been examined[10]. Terminal-stage cancer can be a heartbreaking experience for a patient and their family; not being able to accept death can make the final days an extremely painful time[10]. In various randomized studies and follow-up studies of psilocybin usage in cancer patients who experienced anxiety and depression, the usage of psilocybin was considered beneficial[9,11,12]. In one study, at the 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and antidepressant effects and improved patient attitudes toward death[12]. Psychedelics such as psilocybin help break down the defense mechanisms of an individual in a healthy way - this is why it is considered a "cure-all" for mood disorders (anxiety, depression, and obsessive compulsive disorder)[2,10]. One patient stated that psilocybin made them "lose their fear of death" and improved their end-of-life experience[1]. Providing these relieving therapies to patients with cancer is important for their mental health and might represent a valuable addition to palliative care.

A final usage of psychedelics is in addiction therapy. LSD has developed the worst reputation of all the psychedelics in the Western world but over the past few decades, research into microdosing with LSD has begun again[3]. Microdosing is administering small doses of a drug into one's system to test or experience mild effects and benefits while minimizing adverse reactions that might be experienced with higher doses[13]. Like other psychedelics, LSD alters people's perception of the world and increases their openness to try new things[1,13]. In the case of addiction, LSD's alteration of people's perception makes them more malleable and open to letting go of their addictions[1,2]. In a recent paper, subjects willingly took LSD in a non-medical setting and proceeded to quit smoking by claiming that withdrawal effects felt less severe than past attempts[14]. Such a study would have to be replicated in more controlled settings with appropriate dosing of LSD to be more rigorous; however, this study is promising and implies that LSD may be used in other addiction studies. It is an advertised fact that Bill Wilson, the co-founder of Alcoholics Anonymous, claimed that he was able to combat his addiction to alcohol after he used LSD[15]. He came to believe that LSD could help "cynical alcoholics" achieve a "spiritual awakening" and start on the path to recovery[15]. Thus, further investigation of microdosing with LSD as a treatment for persistent addictions is needed.

Despite all its clinical success, the usage of psychedelics can sometimes have adverse effects. When used in an unsupervised environment there have been reports that people feel like they can fly or can jump off buildings with no consequences[2]. Reports of peyote have been indicated to cause tachycardia and psychosis with threatening hallucinations[1]. High doses of psilocybin have been involved with vascular problems

and rhabdomyolysis[1]. Rhabdomyolysis has been further reported with high doses of LSD[1]. Rare cases of fatal overdoses have occurred with the psychedelic phenethylamine 2,5-dimethoxy-4-bromoamphetamine in the past[1]. Cases of addiction have been mentioned in the sense that people enjoy the level of spiritual elevation they achieve while on these substances, but no accounts of true dependence or addiction have been mentioned[1,2,3]. Other instances of injuries with psychedelic usage are extremely rare[1]. They are one of the safest known classes of CNS drugs as they do not cause addiction, and, importantly, no cases of fatalities have occurred after ingestion of typical doses of LSD, psilocybin, or mescaline[1].

As a future medical practitioner, I believe that the usage of psychedelics in psychiatric therapy should be encouraged. Psychedelics are useful for many therapies as they create a sense of openness in people, which helps them accept feelings and come to terms with past traumatic experiences. Psychedelic usage may be an extremely beneficial therapy for psychiatric patients who do not show improvement with standard psychiatric care or treatments. LSD, Psilocybin, and MDMA are currently being researched as therapeutic aids in several regions of the world and Ireland should be involved as well. Psychedelics are the future of psychiatry, and we must begin their legalization process for medicinal usage.

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Ethical dilemma in Dietetics: Should dieticians engage in paid partnerships?

AOIFE TWOMEY

Introduction

With global shifts towards social media as a new way of communicating and receiving information, medical fields must adapt to trends, to maximise reach for providing accurate, evidence-based advice to the general public and call out or clarify mis-information that can be potentially harmful. We have seen instances of mis-information causing harm in the past. Wellness influencers like Belle Gibson promote dangerous pseudoscience as a cure for disease, where an Australian cookbook author faked having cancer to convince her followers that she cured it through healthy eating habits and exercise. Similarly, in Ireland we have seen The Happy Pear influencers making factually incorrect claims on reducing breast cancer risk. Scandals like these confirm the need for healthcare services and professionals to have a strong social media presence, to monitor and counter unqualified, inaccurate health advice that is rampant throughout the internet. It is critical that social media is used ethically and professionally, to represent dietetics as a profession and field of scientific study.

Paid partnerships are a growing phenomenon, with many looking to pay more for products that are supported by claims or endorsed by credible science, celebrities, or professionals. The classic example is Oral B adverts, claiming to be recommended by dentists. This leads to questions around the acceptability and ethics of health professional paid partnerships with private companies.

If a dietician starts working with one company and really believes in their initial products/ethos, they may be delighted to promote the product and company. However, if the company then launches subsequent products that are less health promoting, the dietician may feel pressured or obliged to maintain their commitment to the company for financial gain and promote a product that they don't really believe in or that lacks clinical and scientific studies to support its clinical efficacy. A dietician's financial relationship with a company may lead to falsehood and bias in dietetic advice. The advice given during dietetic sessions may be influenced by the financial gain of the recommendation, not just the strong scientific evidence supporting the product or supporting the dietary advice given. Naturally, if you know a lot about a particular product, you are likely to recommend it, but this may prevent dieticians from seeking out other products that may be nutritionally equal or even better.

Through endorsements, larger brands can become market leaders, charging premium prices as a result of dietetic endorsement, while other smaller companies and start up's may not have the finances to support financial endorsement from dieticians, though their product(s) may be equally beneficial. This could ultimately undermine future food and supplement innovation and limit market choice for consumers. Dietetics as a profession would quickly become less professional and lose public trust. Companies and private practice dieticians would use each other in a symbiotic relationship to gain followers, customers and new clients respectively, and the honesty and accuracy of the dietetic advice may become diluted. Certain wholefood products not owned by one particular brand such as apples, lentils, carrots, water etc may not be promoted due to lack of potential financial benefit from their promotion. As a result, dietetic advice would be weakened through financial interest, bias and less evidence based. Paid adverts on social media platforms like Instagram and TikTok are often perceived by the public as tacky and unprofessional and could influence and undermine the public perception and respect for dieticians as a medical profession.

National healthy eating guidelines, such as the food pyramid focus on wholefoods and do not advocate branded products. Dietitians endorsing products may mis-lead consumers into thinking they need to buy this protein bar or protein powder to meet protein requirements and evidence based, national healthy

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eating advice would be further undermined. Moreover, marketing may create a sense of guilt amongst parents in particular, who can't afford branded, endorsed products, but want the best for their child. The credibility of dietetics as a profession would be undermined, resulting in even more confusion amongst the public and those with limited nutrition literacy, who may believe this product is essential to keep them healthy, when a key role of a dietician is to educate and empower people to choose wholefood, diverse diets, and adopt a food first approach where possible.

Advertising and social media have huge scope and potential to quickly reach large numbers of people, with varied knowledge and health literacy. It is important that advice shared on these platforms is accurate, unambiguous and not be harmful. Dieticians often work with vulnerable population groups. If a dietician was sponsored by a particular plant-based milk company for example, they could promote it with the intention of only reaching adults, yet social media viewers may mis-understand and give it to their young child, with adverse health consequences. Much of the information and advice dieticians give in clinic is population sensitive and very individualised to socioeconomic and personal context. The primary role of a dietician is to use scientific evidence to give tailored advice to individual patients. If a dietician consciously promotes a particular product for personal gain, taking precedence over the appropriate dietetic advice, then the code of ethical and professional practice for dieticians comes into play. The dietician must enter a client session based on ethical practice and focused on the medical analysis of the patient.

CORU codes of professional conduct and ethics for dieticians set clear rules and standards that must be adhered to in dietetic practice. The guidance states that Dieticians must act in the best interests of service users (1), use social media responsibly (4) , keep professional knowledge and skills up to date (10), act in accordance with the principles of open disclosure (14), demonstrate ethical awareness (22), avoid conflicts of interest (24), and make sure that any advertising is truthful, accurate, lawful and not misleading (26). In following the CORU codes of professional practice, a Dietitian should not engage in paid adverts for personal financial gain where there is a lack of evidence supporting the product or any ethical issues surrounding the promotion of the product. For example, it would be hugely unethical (and unscientific) for a dietician to promote a particular brand of infant formula over breast-feeding, in exchange for financial gain. Similarly, it would be unethical for a dietician to say "do you want your child to be healthy? Then you need x multivitamin." However, the line becomes less clear if the product has a feature that is evidentially superior to competition and the dietician can scientifically justify this recommendation. For example, dieticians may recommend Ready Brek as a suitable breakfast over regular unbranded oats, due to the fact that it is fortified with key nutrients such as iron, an important nutrient in this cohort with common iron deficiency. Drawing the line can be difficult for the individual, so professional practice guidelines are needed and professional enforcement is also required, particularly where personal gain is linked to product promotion.

The scientific approach has informed dietetic research, education and practice and has provided solid and rigorous foundations for the profession to prosper and expand. Science has 'legitimised' the Dietitian profession within modern healthcare[4]. Professional practice cannot be neatly or succinctly defined, if it is to have resonance and meaning across the diversity of dietetics practice. Professionalism is a socially constructed concept, it is multi-dimensional, and it changes across time and place, being influenced by culture and context[3]. Dietetics is a relatively new medical field and our broader social environment is continually changing, posing numerous ethical and practical challenges that need to be considered through a critical, innovative lens. This necessitates expanding paradigms and ways of thinking, educating and being[1]. Dietetics is shifting focus more to the art of practice, and paying more attention to the sociocultural factors within our profession and our education systems, including how we support transitions and socialisation into the profession[2].

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KARAKÖY

Elective Experience - Summer Erasmus Madrid 2022

ADINA ELENA ZAGONEANU

In the blink of an eye I was on my flight home, wondering how two months, which felt like two years, could pass as quickly as two weeks. During the summer of 2022 I was lucky enough to be one of the three DEM3/GEM2 students to participate in an erasmus exchange in Madrid, Spain. This was the first year this programme was launched and I was one very happy 'guinea pig'. There's not a day that goes by where I don't wish I could be back in La Latina, in the heart of Madrid, basking in the scorching heat. Although, on that note, the scorching heat I could do without...

Madrid is the bustling capital of Spain with a population of 3.2 million. That summer it gained 20+ Erasmus students from all over the world who came for clinical electives at Hospital Fundacion Jimenez Diaz, which happens to be the best hospital in all of Spain. The unlucky few (among which we include ourselves) were only there for two months, while others had the privilege of being there for 6 months to a year. You'll find medical schools around Europe aren't as accepting of other universities elective programs and curriculum, that's why our exchanges are so short lived. However the beautiful unspoken rule of knowing your time is limited, is that everyone is generous with their friendship and their time. You take nothing for granted and make the most of every day. A simple hello outside the lockers turns into exchanging life stories over lunch and being friends for 10+ years by dinner, sipping tinto, sharing tapas and laughing a little too loudly over inside jokes in Span-glish.

My first rotation was paediatrics and I got to experience paeds emergencies, inpatient ward rounds, outpatient clinics and neonates. Dermatology was my second rotation which included out-patient clinics and minor-procedure surgeries. A day in the life included strolling through the streets of La Latina at 7:30am, coffee in hand and praying the 14 degrees weather will last as long as possible. From there you'd cross La Plaza Mayor and catch the metro at Plaza del Sol to Moncloa and wonder how is it possible for a public transport system to be ever-so punctual? Hospital placement was from 8am to 3pm and it depended on your specific rotation schedule and sometimes included hands-on tutorials on suturing and microscope assisted anastomosis creation with the other erasmus students.

The first two weeks of my elective felt like being in the front row at Wimbledon, only a little less glamorous. Your head snapping left and right trying to keep up with conversations, processing what was previously said, only to anticipate the next response, between doctor and patient. There's something very special about hitting the two-week language-barrier watershed. That's when all of a sudden, your brain magically adjusts to the speed of conversation and you understand without needing to feed the constant feedback loop of translation. By the third week you're confident to ask questions and respond, in as best an accent that you can muster. By the fourth week you feel like a local, using colloquialisms and speaking to the pace of the latest reggaeton single.

During my paediatric placement I was incredibly impressed to see how quickly patients got triaged and managed through paediatric emergencies and how smoothly the work flowed. This was mostly thanks to paediatric emergency departments being separate to general a&e and also the digital medical platform used by the hospital. On this platform doctors and parents/patients could have access to the patient's file including medical history, their prescriptions, past/future appointments and scans. My favourite aspect of paediatrics was assisting in paediatric allergy clinics where children would be given management plans in accordance to their allergies. Regarding children with food allergies, micro-doses of the allergen would be introduced in their diet to help the child build tolerance to the substance over time (6m - 1 year). For children with pollen related allergies, they were prescribed either oral medications daily, or IM injections to be done at home, to help the child build their tolerance to allergens from September - March to not have bad flare ups during the spring and summer season. Dermatology for me was the creme de la creme, excuse my French. I got to assist in dermatology clinics, I sat in on lectures and MDTs. Most importantly I got to help with minor surgical procedures such as SCC and BCC removals and suturing.

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The Spanish healthcare system was quite different to the Irish healthcare system in that doctors are allocated their medical specialties after finishing their final year medical exam (MIR). We are very fortunate in Ireland to be able to pursue whatever training scheme we desire by working in the field and gaining experience. Training schemes in Spain last on average four years after which doctors can pursue fellowships and PhDs. The regular work schedule for doctors is 8am - 3pm except for those who are on call, and the frequency of on call depends on your speciality of choice. The role of doctors also is different and only includes consulting patients and performing physical exams. All other tasks such as phlebotomy, cannula and catheter insertion are performed by nursing staff. I think it's better for doctors to have the skills to perform all tasks, however I understand why in Spain they allocate jobs differently. All in all - I've yet to think of any negative traits of the Spanish healthcare system. It's a system which flows seamlessly for optimal patient treatment and comfort, within the healthy, work-life balanced-based capabilities of the medics and staff, and it therefore supports a happy and healthy community.

Thanks to my experience I've met so many amazing future medics and Spanish medical professionals that I keep in touch with to this day and hope to continue doing so.

I count down the days to becoming qualified so I can return even for a short while and embrace the culture and the medical work in Spain, once again.

Bed Numbers

SINEAD DART O'FLYNN

On my first ever medical attachment
Mercy University Hospital
I scurry along the cold corridors
Seeking out approval
Alone for a tutorial
With a consultant doctor
Where are my friends
Why didn't they show up
Were they wiser than I

Consultant doctor:
"Take a history from XYZ
in bed number A on ward BC"
Eager beaver
Wanting to impress
I hurry off in my purple scrubs
I hit the lift on floor two
Shit
What bed number did he say
Panic ensues
What f*cking bed number did he say

He'll think me incompetent
He'll think me a fool
I'll be shame walked
in front of the school of medicine
Branded a tool

Student nurse guide me
And we figure it out together
All though I'm not sure
What bed number did he say
I say a prayer
anyone up there who'll listen
I don't even believe

Relief as consultant walks in
I have the right patient
Thank god

UCC

PAEDIATRICS

Future Frontiers in Paediatric Oncology

DANIELLE BELEUTZ, SYDNEY BRANNEN, PÁDRAIG CRONIN, COLLEEN HAUGHEY

Introduction

Paediatric oncology is the field of medicine relating to the care and treatment of childhood cancers. Over the past two decades, the remission rate has been increasing due to improved treatment methods[1]; however, a number of aggressive forms of malignancy still affect this cohort[2]. These rarer forms of cancer do not respond well to conventional treatment, presenting a significant challenge for paediatric oncologists due to their unique genetic profile and rapid progression. This paper seeks to explore two new frontiers in paediatric cancer treatment: the fields of genetic testing and targeted treatment strategies. Combined, both of these domains not only present a promising approach toward treating childhood cancers through personalised medicine, but also earlier detection leading to improved survival rates.

Epidemiology

The global incidence of childhood cancer is 140-155 million per year in those under 15, and 210 million per year in those aged 15-19[3]. The most common diagnostic groups are leukaemias (34%), brain tumours (23%), and lymphomas (12%)[4]. Childhood cancers are a significant cause of morbidity and mortality, accounting for 23% of deaths in children aged 4-15. Malignant neoplasms have been identified as the second leading cause of death in this age group[3,5]. However, with advances in modern medicine, the survival rate of paediatric cancers is 83%, a large improvement from the 20-30% in the pre-chemotherapy era of the 1960s[3,6].

Genetic Testing

Genetic testing is a rapidly emerging field with applications in a variety of cancer predisposition syndromes (CPS)[7]. CPSs are caused by germline mutations in tumour suppressor genes, growth factors, and DNA repair genes1. Approximately 10-15% of children with cancer will have an underlying CPS[7].

Furthermore, studying patients with a potential CPS is important in the development of discovery of inheritable mutations, cancer screening, treatment, follow-up protocols, and family support[8]. A limitation to the integration of genetic testing into the referral and management of patients with potential CPSs is that of the provider: research has shown that paediatric oncologists do not feel confident regarding the genetic testing procedure, and instead prefer to refer patients to a geneticist[9].

Current tools for genetic analysis include next-generation sequencing, a high-throughput method which allows for quick sequencing of a desired genome that is both sensitive and accurate[10]. The availability of sequencing technology throughout laboratories has widened the spectrum of its use, including research applications, clinical trials, and clinical investigations[11].

Targeted Treatment

The discovery of various CPSs has allowed for the development of targeted therapies for paediatric oncological conditions, increasing the standard of care by removing the need to use chemotherapeutic and radiotherapeutic options and therefore its short- and long-term side effects[12]. Immunotherapy is an effective therapy which aims to target a patient's individual mutation with antibodies to nullify its function[13], thus reducing toxicity compared to conventional methods[14]. Current practice utilises immunotherapies such as blinatumomab and chimeric antigen receptor T-cells (targeting CD19 and C22 respectively) for refractory B-cell precursor acute lymphocytic leukaemia[14].

In recent years, Clustered Regularly

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Interspaced Short Palindromic Repeats (CRISPR) therapy has developed as a potential targeted therapy method. CRISPR systems exist naturally in a broad array of bacterial species, which work to splice DNA at specific locations and sequences in order to allow for genome editing[15]. Tangible clinical applications of CRISPR include diagnosis by recognition of microsatellite mutations, which are diagnostic markers in particular cancers[15]. Furthermore, ex-vivo CRISPR therapy would involve engineering T-cells to attack a particular target, a method currently being used in research applications to date[15]. The ideal goal would be to effect in-vivo cell change using CRISPR, allowing for direct tumour cell therapy and disruption of the tumour promoting gene within[15]. However, there are multiple variables that limit the applicability of CRISPR as a clinical therapy in the current moment, including proper delivery of the CRISPR machinery directly to the tumour cells, and the researcher's ability to artificially edit a cell genome within a cell that naturally resists editing[15].

Ethical Considerations of Paediatric Oncology Research

The implementation of genetic testing and targeted treatments into the clinical environment is not without significant challenges. The ethics of cancer care is a broad and complex aspect of oncology which is further compounded when it pertains to the care of children. Research into the treatment of cancers often deals with the care of individuals who are vulnerable due to the emotional and physical limitations placed on the person by the diagnosis. Thus, conducting research into novel treatments on this cohort must ensure the patient is fully aware and consents to participation. This leads to an overlap of two fields with fundamentally different aims: patient treatment and cancer research. Patient treatment places an emphasis on the care and survival of the patient, with minimal consideration for developing new knowledge[16,17]. In contrast, cancer research prioritises the pursuit of knowledge and solutions, with less regard for the therapeutic benefits[16,17]. This overlap is a grey area which is hard to reconcile, particularly when weighing against the emotional care of the child and parents.

To confront this, paediatric physicians and nurses have identified three key areas of consideration: (1) positive communication with the patients and their family, (2) acknowledging the vulnerability of the patient, and (3) balancing the best interest of the patient and their parents in their respective roles in a parent/child relationship[18]. Such considerations can allow for the safe integration of both patient care and cancer research within paediatric oncology, developing a mutually beneficial approach for the child and their family.

Conclusion

Ultimately, personalised medicine such as genetic testing can aid therapeutics in paediatrics by providing an avenue for targeted treatments. Genetic testing could identify childhood CPS, with direct clinical therapeutic applications. Technologies such as CRISPR and immunotherapies can alter current practices to reduce current regime toxicities. However, ethical considerations in balancing patient treatment and advancements in cancer research play a major role in the implementation of novel therapies. An understanding of genetic testing and targeted treatments could create a nuanced therapeutic regime in paediatric oncological patients that centres around each child as an individual.

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UCC OBGYN

Emerging Areas of Personalized Medicine in Obstetrics & Gynaecology: A Narrative Review

ROXANNE H. LEUNG, ALYSSA BELFIORE, HANNAH WHIBBS, EMMA WILSON, HOYANG SEO, SYDNEY ROTMAN

Abstract

IMPORTANCE: The focus of obstetrics and gynaecology (OBGYN) is women's reproductive health. Many significant challenges in the field of OBGYN stem from limitations in screening, diagnostic, or treatment options. Conditions that are poorly understood, such as pre-eclampsia or endometriosis, offer few management options or prevention strategies. In recent years, growing interest and advancements in personalized medicine have led to a deeper understanding of the aetiology and pathophysiology of OBGYN conditions, potential targets for intervention, and novel approaches to management. The aim of this review is to briefly describe some of these emerging areas of research and clinical uses.

OBSERVATIONS: Personalized medicine in obstetrics is a foundational concept underlying routine prenatal care. It also drives ongoing research in areas such as advanced assisted reproductive technology, screening for medical complications during pregnancy, and in utero foetal treatment of congenital diseases. In gynaecology, developments in our understanding of the determinants and mechanisms of conditions such as endometriosis and menopause have illuminated potential avenues for improved diagnosis and more individualized approaches to treatment.

CONCLUSIONS AND RELEVANCE: Personalized medicine in OBGYN is a flourishing area of research with the potential for significant clinical benefits. Ongoing research into OBGYN disease processes that are poorly understood are beginning to identify potential novel diagnostic and treatment options for the future. With endless potential to improve the health outcomes of women and children, personalized approaches to screening, diagnosis, and management are worthwhile investments.

Introduction

Obstetrics and Gynaecology (OBGYN) is the field of medicine that focuses on women's health, including pregnancy and its associated complications, childbirth, and conditions involving the reproductive organs. As the field of personalized medicine has grown across all areas of medicine, advancements specific to OBGYN have also been developed into novel or potential clinical applications. Personalized medicine eschews the presumption of a "one size fits all" management approach and aims to develop individualized and targeted therapies for patients by understanding and leveraging the pharmacogenomic, biological, and environmental determinants of a condition.

A better understanding of the aetiology and pathophysiology of conditions in OBGYN have led to exciting potential applications for personalized medicine in OBGYN. For example, two areas of focus for personalized medicine in OBGYN include infertility and gynaecological cancers. According to the World Health Organization, 10 to 15% of couples worldwide experience infertility in their lifetime[1]. Meanwhile, 70% of in-vitro fertilization cases fail per cycle in the United States[2]. Personalized medicine in advanced assisted reproductive technologies (ART) is an emerging area of focus aimed at improving these outcomes[3,4]. Genetic subtyping of gynaecological cancers is another potentially significant area for personalized medicine in OBGYN. Treatments tailored to a

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patient's genetic subtype have been shown to improve survival outcomes when used in conjunction with traditional chemotherapy[5]. In this narrative review, we briefly explore in greater detail some of the existing applications of personalized medicine in OBGYN and emerging areas of research.

Personalized Medicine in Obstetrics

A personalized, multi-modal approach to routine obstetric care combines patient characteristics, advanced imaging, and genetics for early detection of foetal pathologies and risk stratification during pregnancy. For instance, the combination of maternal factors with ultrasound-based parameters, including estimated foetal weight and uterine artery pulsatility, is used to identify antenatal pregnancies at risk for small for gestational age (SGA) neonates. This allows for early monitoring of SGA foetuses and determines the appropriate frequency of follow-up assessments[6]. Individual patient factors are also increasingly used in advanced ART to increase success rates and prevent foetal disease. One example is pre-implantation embryo genetics, which involves genetically testing embryos for chromosomal abnormalities before implantation, allowing for medical decisions and interventions tailored to the genetic characteristics of the individual(s)[7]. Non-invasive perinatal testing during pregnancy can identify chromosomal abnormalities, copy number variants, or single nucleotide polymorphisms (SNPs); furthermore, whole genome sequencing of maternal blood is an effective indicator of aneuploidies[8,9] and monogenic diseases such as beta-thalassemias[10]. Similarly, comparing foetal DNA to the SNPs on existing electronic records is useful for the prediction of gestational diabetes before its onset[11].

Identifying maternal biomarkers is another tool used for the early detection and treatment of obstetric diseases in utero. One study demonstrated that altered angiogenic biomarkers, placental growth factor, and soluble fms-like tyrosine kinase 1 (sFlt-1) can be used as indicators of pre-eclampsia, hypertensive disorders during pregnancy, and foetal growth restriction[12]. Another paper described the potential for in utero precision gene-editing in sickle cell disease[13]. Improvements in diagnostic precision are also paving the way for early and targeted interventions in obstetrics, with tools such as nanotechnology and exosomes[14].

Dedicated research centres such as the Irish Centre for Maternal and Child Health Research (INFANT) are leading the frontiers of personalized medicine research in OBGYN to address knowledge gaps, quality improvement, and the clinical experience of parents[15]. For example, the Pregnancy Loss research group was awarded the HSE Open Access Research Award for qualitative research on antenatally-diagnosed fatal foetal anomalies and the experience of parents[16]. Taking a personalized approach to obstetric care has positive implications for disease prevention, detection, and treatment, leading to better maternal and foetal outcomes.

Personalized Medicine in Gynaecology

Recent advances in technology have fuelled research into personalized approaches in the diagnosis, prognostic prediction, and treatment optimization of gynaecological conditions[17]. For example, computer-aided histopathologic characterization of endometriotic lesions may lead to improved diagnostic and prognostic accuracy of endometriosis. In one study, the use of a specialized form of mass spectrometry coupled with statistical modelling enhanced the classification of endometriotic lesions with 98.8% accuracy[18]. Another study quantified cytokeratin and CD10 markers in epithelial and stromal cells from excised endometrial lesions and found a correlation between total endometrial cells and pain ratings[19]. These developments in endometriosis research contribute to better identification of disease mechanisms. According to Dr. Mette Nyegaard, a professor of Personalized Medicine at Aalborg University, these advancements could “pave the way for enhanced risk prediction tools and the emergence of personalized treatment options”[20].

Personalized medicine also plays a role in assessing the risk and candidacy for hormonal therapy in postmenopausal women. The Women's Health Initiative in the United States has suggested that a woman's individual characteristics, including age, time since menopause, symptom severity, and genetic predisposition can influence the efficacy of hormonal

therapy[21]. The concept of personalized medicine in the management of menopause aims to identify women who are more likely to benefit from hormone therapy and allows for tailored treatment approaches that enhance efficacy and safety. Additionally, incorporating patient-centred outcomes such as quality of life into the clinical decision-making will further enhance the care provided by gynaecologists managing menopause. When considered in the risk-benefit ratio, these individualized factors have been shown to directly impact treatment compliance of hormonal therapy[22].

Future Directions

Women's health has advanced substantially throughout the 21st century with increased research interest in OBGYN conditions[23]. As such, there are many exciting new technologies being investigated to allow for personalized care. For example, novel personalized contraception that is reliable, affordable, requires fewer medical visits, no procedures, and provides women with more control over their contraceptive care are being developed. These include a once-a-month pill, micro-array patch, and a 6-month injection[24]. Another example of an innovation that will improve safety for mothers and new-borns is an artificial intelligence (AI) powered portable ultrasound machine[25]. Many wealthy countries and hospitals have the staff and resources to scan and interpret results for pregnant mothers; under-resourced areas or rural communities may not have access to these same resources. AI powered ultrasound technology could provide the imaging assessments necessary in resource-limited areas and guide the appropriate management of obstetric complications[25]. As more funding and research is directed towards personalized medicine in women's health, we will see advancements in conditions that are difficult to identify and treat, thus improving reproductive health for women globally.

Conclusion

Interest in personalized medicine has led to advancements across all areas of medicine, resulting in targeted diagnsostic and management approaches. Within OBGYN, progress manifests in heighted success rates in assisted reproductive technologies, screening and diagnostic test accuracy in significant obstetric complications, enhanced accuracy of screening and diagnostic tests for significant obstetric complications, and novel therapeutic modalities for challenging conditions. With time, the impact of personalized medicine in OBGYN will only enhance reproductive care and contribute to better outcomes in women and children's health.

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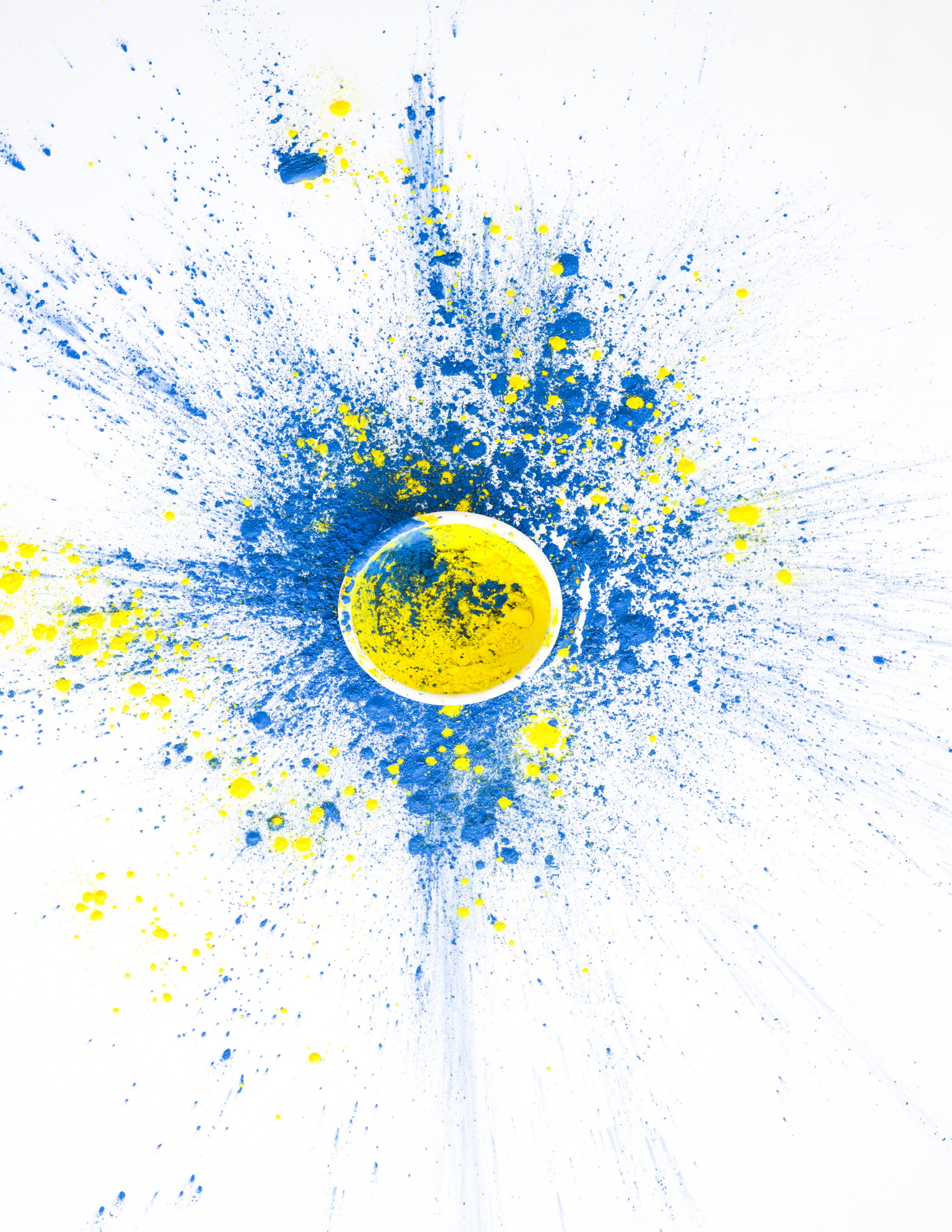


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Enter Modius: Neurovalens's Innovative New Solution to Insomnia

ANDREW ISKANDER

Background

Adequate sleep is an important aspect of a healthy lifestyle that increasingly seems to evade many. Factors like elevated stress and poor sleep hygiene are some of the primary culprits behind this, and the consequences they can have on patients' health are hard to overstate. Insufficient sleep has been documented to have adverse long-term effects on patients' cardiovascular health, immune systems, and mental well-being, among many other facets of health[1]. Given this, patients with insomnia are at significantly elevated risk of developing these negative health outcomes over time. Insomnia is defined as difficulty with sleep onset or maintenance with associated daytime deficiencies, such as poor concentration. In Ireland, it has been estimated that up to 15% of the population struggle with this potentially debilitating disorder, surpassing some other European populations[2,3,4]. Further complicating things, the management of this disorder can be quite difficult and inconsistent. The pharmacological options we currently have at our disposal tend to either have limited efficacy, like melatonin receptor agonists, or carry the risk of dependence, such as benzodiazepines1. As for non-pharmacological therapies, our options are extremely lacking, with cognitive behavioural therapy being the only such treatment currently recommended by the Centers for Disease Control and Prevention (CDC)[1].

With that being said, this may not be the case for much longer. The gap in our management repertoire of insomnia may soon be shrinking with the recent FDA approval of Belfast-based Neurovalens's Modius SLEEP technology, which boasts the ability to help regulate circadian rhythms via electrical stimulation of the hypothalamus without a single drug needed[5]. Not only is this device non-pharmacological, it is also remarkably totally non-invasive, meaning the risks and side effects of using it are greatly reduced. Another important benefit is the device's ease of use. All patients need to do is simply wear the headset and turn it on for 30 minutes of totally painless neural stimulation an hour before sleeping – no need to keep it on while asleep[5]. Patients can even continue with activities like reading while the device is active. The simplicity and comfort of the process is an essential aspect of the Modius's appeal for patients and clinicians alike, as it makes it considerably less likely that patient compliance will be a major issue.

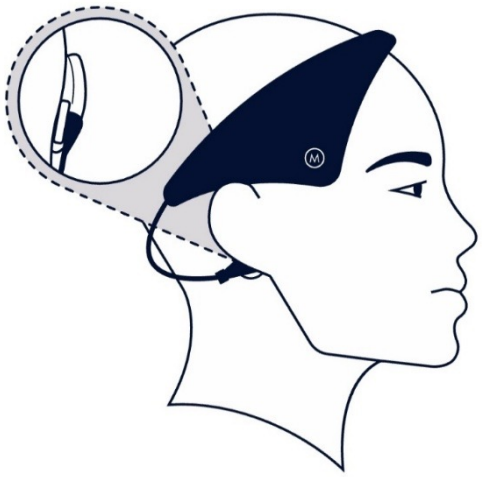

Figure 1 - How to wear the Neurovalens Modius SLEEP headset[5]

Mechanism of Action

Even more interesting, however, is how this technology works. The main target of the headset's neural stimulation is the suprachiasmatic nucleus, which is located on the anterior aspect of the hypothalamus and is responsible for regulating the body's sleep-wake cycle, also known as the circadian rhythm[5]. The usual challenge with accessing this region is that it is anatomically quite deep within the brain. This makes it extremely difficult to stimulate without the use of an implant, which would of course be very invasive and thus exacerbate both the risks and cost. The technological innovation Neurovalens's Modius uses to circumvent this obstacle is as elegant as it is potentially useful: it uses our understanding of neural pathways to first target peripheral nerve fibers that are both superficial enough to be easily accessed and project to the ultimate target structures. In this particular case, the initial target of the headset is the peripheral branches of the vestibular nerve (one of the two major branches of cranial nerve VIII), which

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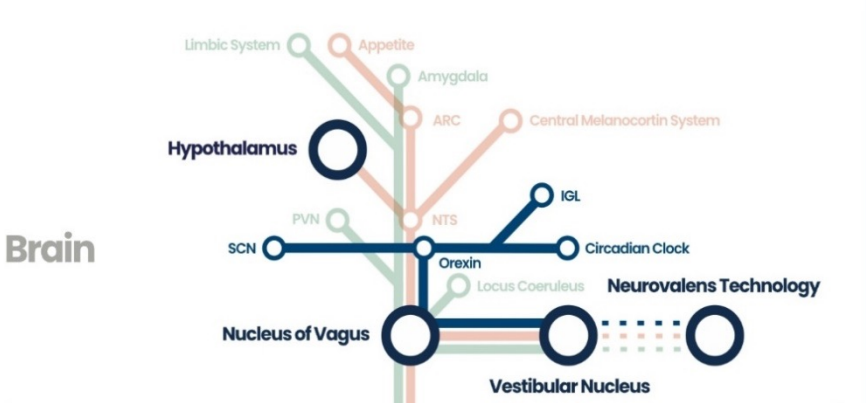

Figure 2 - The neural pathway used by the Modius headset to stimulate the suprachiasmatic nucleus (SCN: suprachiasmatic nucleus, IGL: intergeniculate leaflet)[5]

terminate at the mastoid process inferoposterior to the ear canal. Stimulating these nerve fibres propagates the electrical signal to the medial vestibular nucleus of the medulla oblongata, from where it proceeds to the hypothalamus[5]. In this way deep brain structures like the suprachiasmatic nucleus can be safely targeted for stimulation without any invasive procedures or drugs, so far as there is a known and accessible neural pathway that can direct the signal to it without adversely stimulating unintended brain structures.

The theory of this mechanism posits it will help normalize circadian rhythms and allow patients to have prolonged and higher quality sleep, and the available data suggests it does exactly that. A randomized controlled trial published in 2020 by S. Goothy and J. McKeown, the latter of whom is the founder and CEO of Neurovalens, sought to find the effect of electrical vestibular nerve stimulation on the sleep pattern of 20 patients with insomnia[6]. Specifically, they measured the change in subject scores on the Insomnia Severity Index (ISI), a standardized self reported questionnaire used to ascertain the severity of patients' insomnia. After just 14 days of regular use of the device, the mean experimental ISI scores were found to have dropped significantly from their baseline counterparts. Specifically, the mean ISI score dropped from 15.7 ± 4.7, which is classified as moderate insomnia, to 8.15 ± 3.6, which is considered sub-clinical. Furthermore, mean self-reported restfulness in the mornings on a 0-4 Likert scale increased from 1.6 ± 0.63 at baseline to 2.67 ± 0.56 during the second week with no reported adverse events[6]. This data is quite encouraging, and suggests that Neurovalens's Modius SLEEP technology could provide a viable alternative to insomnia management, though more research should (and seemingly will) be done to reproduce these findings[6,7].

Future Directions

The publication of this clinical trial was followed by the recent FDA approval of the Modius SLEEP device, meaning it can now be sold commercially and potentially provided via medical insurance with the prescription of a doctor. Speaking on this, Neurovalens CEO Dr. Jason McKeown said "Having the Modius Sleep technology as a certified medical device for the treatment of chronic insomnia is a landmark step for the company as we focus on future growth in the US market. Most other products on the market measure symptoms of insomnia, but Modius Sleep is a non-invasive device that actually treats the underlying issue, improving the lives of our patients[8]." Moreover, insomnia is not the only condition Neurovalens intends to address using this technology, and is investigating its therapeutic use for patients with anxiety, obesity, and even type II diabetes[5]. While we have yet to fully understand the potential of this technology or how useful it will truly be in a clinical setting, one thing remains clear: it certainly seems promising.

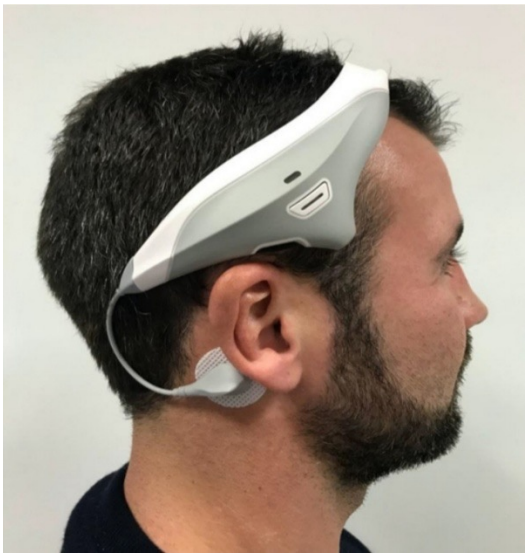

Figure 3 - Subject using a Modius headset[6]

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A Snapshot of Personalized Medicine in Palliative Care

HAKHAMANESH BEHMANESH

Palliative care is an interdisciplinary care system that addresses the physical, emotional, social, and spiritual needs of patients and their families facing serious illness. It includes a team of medical professionals who work together to improve patient overall quality of life. While almost half of those who die in the US receive hospice services, many hesitate to enrol early due to the requirement to forgo curative treatment. To meet this challenge, unlike hospice care which may require forgoing curative treatment, palliative care services can be provided alongside curative treatments. When disease-modifying treatments are no longer an option, the traditional roles of medical team members change, with palliative medicine experts taking on a larger role in patient care. This comprehensive care can include managing pain and symptoms, providing social services and counselling, and assisting with daily living activities and spiritual support, among other services. Overall, palliative care services aim to enhance existing care services and involve additional support from family and community groups.[1]

The EU Health Ministers in December 2015 defined personalized medicine as:

"A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."[2]

Personalized medicine tailors medical treatment and care to individual patients based on their unique characteristics such as genetics, lifestyle, and environment. Such interventions are more effective and have fewer side effects compared to a one-size-fits-all approach. For example, in the management of pain in palliative care, traditional practices may prescribe a standard dosage of pain medication for all patients with advanced cancer, without accounting for factors such as genetic variations and individual preferences for pain relief.[3]

In recent decades, palliative care and oncology have developed together to meet the complex needs of cancer patients. Indeed, many palliative care specialists aim to work with oncologists to ensure comprehensive care for patients with advanced-stage cancer. This comprehensive care can include improving patient comfort, improving symptom management, and optimizing end-of-life care. The integration of palliative care in cancer treatment must be tailored specifically to each cancer type. For example, if a patient has an ALK fusion with advanced non-small-cell lung cancer, immediate anti-ALK therapy should be prioritized, even if the patient is in poor health. This may result in extended survival and multiple treatment options, reducing the need for early palliative care. On the other hand, if a patient is diagnosed with a more aggressive form of cancer like SMARCA4-deficient ovarian or lung carcinoma, early palliative care may be necessary despite the patient's initial good health due to the poor prognosis. This method emphasizes the importance of personalization and timing in incorporating palliative care, aligning with the broader goals of precision medicine in oncology.[4] There are also other ways in which personalized medicine intersects with palliative care:

1. Tailored pain management: a tailored pain management approach in palliative care involves using a combination of medications and non-pharmacological interventions, such as physical therapy, massages, or acupuncture, to help manage pain effectively. On the other hand, personalized medicine involves using a person's genetic makeup to tailor their medical interventions and treatments. In pain management, personalized medicine in palliative care will focus on the identification of genetic mutations or changes that influence the disease progression or drug metabolism. By understanding a person's genetic predispositions, the multidisciplinary team caring for the patient can optimize pain management interventions to better suit the patient's individual needs, leading to improved pain control and overall well-

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being.5 One example of personalized medicine leading to better pain management outcomes in palliative care is a study conducted by Wong et al. (2022), showing how genetic testing for variations in the cytochrome P450 (CYP) enzymes, which play a significant role in the metabolism of opioids, can improve pain management in hospice patients. By identifying patients with specific CYP genetic variations, the hospice team was able to personalize pain management strategies and adjust medication dosages accordingly. The results of the study showed that by tailoring medication dosages based on genetic differences, patients experienced improved pain control with fewer side effects, hospitalizations, and ER visits. This study suggests that personalized medicine techniques that involve genetic testing can improve palliative care and lead to better outcomes.[6]

2. Patient-centred decision making: personalized medicine emphasizes a shared decision-making approach that involves patients, their families, and healthcare professionals collaborating to make decisions about patient care. In palliative care, it involves understanding the patients' wishes, values and preferences regarding treatment options and end-of-life decisions. Promoting patient autonomy and improving the overall quality of care is an important aspect of patient-centred care and palliative care.[7] An example of personalized medicine facilitating understanding patients' values and preferences is the case study of the CancerLinQ platform developed by the American Society of Clinical Oncology. This is a big data platform, which helps oncologists understand patients' values and preferences by analysing real-world data to tailor treatment plans based on individual characteristics and preferences. By considering factors such as treatment side effects, quality of life, and treatment goals, this results in more patient-centred care that aligns with each patient's unique needs.[8]

Personalized medicine empowers doctors to tailor treatments to individuals by considering the unique interplay between an individual and their disease. It is a constantly advancing, interdisciplinary field with broad implications.[3]

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