UCC smj

University College Cork
Student Medical Journal

UCC
MEDICAL RESEARCH
AND
TECHNOLOGY SOCIETY

First Edition

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

"Where Finbarr taught let Munster learn" .

All published articles are decided by a panel of peer and faculty reviewers from University College Cork. Any opinions communicated within the journal are the authors' own and do not necessarily reflect the opinions of the UCCsmj or of the UCC School of Medicine. The UCCsmj team, including authors, editors, and publishers, do not accept any responsibility for any loss or damage arising from actions or decisions based on information contained in this publication; ultimate responsibility for the treatment of patients and the interpretation of published material lies with the medical practitioner. The statements and opinions expressed are those of the authors and the inclusion in this publication of material relating to a particular product, method or technique does not amount to an endorsement of its value or quality, or of the claims made by its manufacturer. All permissions were obtained.

Medical Journal Lead,
UCC Student Medical Journal,
School of Medicine and Medical Science,
Brookfield Health Science Complex,
University College Cork, College Road, Cork, Ireland
Alternatively, an email can be sent to
submissions.mrt@uccsocieties.ie
This current volume can be accessed at:
https://submissionsmrt.wixsite.com/website

ISSN (Online): 2737-7237

Foreword

In an ever-changing world with complicated multifactorial problems, now more than ever it is pivotal to encourage students to problem solve. By partaking in research, students can engage with issues in their communities, and find effective evidence based solutions on a local and global level. They have the potential to contribute to new knowledge that has not yet been discovered, and try to address some of the world's complex problems.

The UCC Student Medical Journal provides a space for students to think outside the four walls of the lecture hall. Through all stages of this journal's process, whether it be the research itself, writing, or peer-reviewing, students are pushed to ask critical questions. Concurrently, this opportunity gives faculty the chance to connect with enthusiastic students, and give guidance that will help shape the next generation of healthcare.

One of our main goals is to stimulate more student participation in medical research at UCC. Not only will earlier research exposure engage students in specific medical fields to further shape their interests; it will allow students to become more critical analyzers and ultimately be better advocates for their future patients. Additionally, we are hoping to make research a less intimidating task at introductory levels, and give students foundational skills for their future research experiences and publications.

During a time of great uncertainty, we are proud to provide this opportunity for students to share their thoughts on the current and future status of healthcare. Our experiences and insights help us grow in our understanding of humanity, which is where quality research questions lie. This edition discusses the ethical dilemmas arising from the first pandemic in a century, travels to all parts of the world to inquire about global equity, and reviews critical questions at the forefront of medicine.

We would like to thank the UCC School of Medicine along with the Medical Research and Technology Society for their support of this journal. Furthermore, we would like to thank students involved in the peer review process, and those both published and unpublished in this edition. Lastly, we would like to thank faculty for reviewing submissions and giving their expertise, as well as allowing students to engage in research projects.

We hope with the further pursuit of research, students will grow in their personal and professional development, as well as grasp new insights to last throughout their long and successful careers.

Best,

Ciara O'Donoghue
Robert O'Shea
Samin Abrar



Address On Student Wellbeing During COVID

Dr. Aisling Campbell
Consultant Psychiatrist, Cork University Hospital

Medical students are returning to their studies in Autumn 2020 with a mixture of trepidation and relief, having already endured a very difficult time. For first years, the anxiety surrounding Leaving Certificate and release of grades has been extremely stressful. For most other students, the last academic year was cut short in a dramatic fashion in the context of huge anxiety about COVID, and summer plans for almost all students were cancelled –for most students it has been very difficult to carve out an enjoyable routine with no job and no holiday and the added stress (for many) of being stuck at home. The weeks before the reopening of the University will have been anxious ones also – for most students it will be a relief to return to the campus and to the necessary social contact with peers, but return to hospitals brings further anxiety about contracting COVID, as well as the understandable concerns about gaining adequate clinical experience.

So how to cope during what will be a year full of unknowables? First of all, it is important to acknowledge that your fears and concerns are shared by very many all over the world. You are definitely not alone. All medical schools have been grappling with the same issues, and all medical teachers want to ensure that students have the appropriate knowledge and competencies. You can rest assured that this is the priority for your teachers – while ensuring that you are as safe as it is possible to be. No university can completely reduce the risk to students of contracting COVID. But a lot of work has already gone on behind the scenes to make sure the environment is as safe as possible. Remember this - that others have anticipated your fears and have done their best to reduce risk – and try to move on. You cannot learn if you are worrying constantly, when in reality there are others with the responsibility of doing that worrying for you.

You will at last be back with your classmates on campus and on clinical sites. Try to enjoy the collegiate aspect of university life. Yes, everyone has to rethink their personal space these days, but that does not mean that conversation and social interaction cannot continue. Try to have whatever personal interaction is safe – and keep use of social media to a minimum unless you need to access it for learning purposes.

Try to have a routine – there may be more time now to spend on self-directed learning and it can be difficult to use this time well. Plan out your week of study in advance and stick to it – by definition that means making your goals manageable. Build in some flexibility to your timetable – there will be days when you don't achieve your goals, and that is fine – have space in the week to reschedule those goals. It goes without saying that taking breaks and interspersing your studies with other activities is really important. Outdoor activity is very low risk, from the COVID perspective – there is nothing like going for a run to clear your head!

Again, stating the obvious but excessive use of alcohol, and of recreational drugs is a very bad idea. Try to get some escapism through other means that don't impact your liver or your brain. You need a clear head now more than ever.

Finally, remember that we have all had to reset our awareness to take account of invisible pathogens – but they have always been there, we just have never before had to take them so seriously. It has been a kind of trauma to be faced with the reality that many aspects of life are unpredictable and beyond our control. We all have to find a way of living, working and studying with this circumstance; if you can have some control over the smaller aspects of everyday life, the bigger, less controllable aspects will stay in perspective. Doing a small research project on COVID might be one way of developing a sense that you have some control over it! Eventually the anxiety will diminish and COVID will become part of everyday life. And do remember that this is one of the biggest healthcare challenges the world has ever known (although it must be acknowledged that there are plenty of other equally serious but less well publicised ones) and if you can cope with this, you will be well equipped to deal with the future stresses which you will undoubtedly meet in your future careers.

Acknowledgements

Founders and Co-Editors in Chief of Content

Ciara O'Donoghue
Robert O'Shea

Editor in Chief of Design

Samin Abrar

Cover

Asmita Roy,
Brac University,
Bachelors in Biotechnology, 1st year

UCC School of Medicine

Research and Postgraduate Affairs Committee (RPAC)

Members of the Medical Research and Technology Society

Adina Elena Zagoneanu
Shivika Marwaha
Nicola Mitchell
Mark Llewellyn
Ribh Ardern
Savni Kodilkar
Nicole Martinez Herana
Ciara Gavin
Eibhlis Myers
Joan Omosefe Osayande
Arnav Mahajan

Faculty Reviewers

Dr. Colm O'Tuathaigh
Dr. Ken O'Halloran
Dr. André Toulouse
Dr. Colin Bradley
Dr. Henry Smithson
Dr. Tony Foley
Dr. Elaine Walsh
Dr. Michael Prentice
Dr. Collette Hand
Dr. John Mackrill
Dr. Dervla O'Malley
Dr. Pat Henn

Peer Reviewers

Samin Abrar
Ramesha Ali
Jasmine Aziz
Ramya Baskaran
Ali Abdulghani Binabdi
Taylor Faith Carmichael
Kareem Choucair
Ioana Tereza Florica
Becca Fritz
Ciara Gavin
Victoria Goodall
Liam Grainger
Arlene Leah Gutman
Hakimah Abdul Hamid
Kirk Hartley
Saleem Kamalodeen
Oleksandra Kaskun
Leah Komer
Simran Sarabjit Kundu
Stanley Lee
Shivika Marwaha
Andrew Mazurek
Aoife McDonagh
Chelsey Minehane
Avnee Nulkar
Eileen O'Connor
Maria O'Sullivan
Joan Omosefe Osayande
Yukta Ramesh
Melissa Shiff
Shivali Sood
Habiba Suleman
Aoife Jones Thachuthara
Daniel Thomas
Ashwini Tittawella
Annabel Umeh
Sophie Walker
Fionnuala Wilson
Adina Elena Zagoneanu
Xianghan Zheng

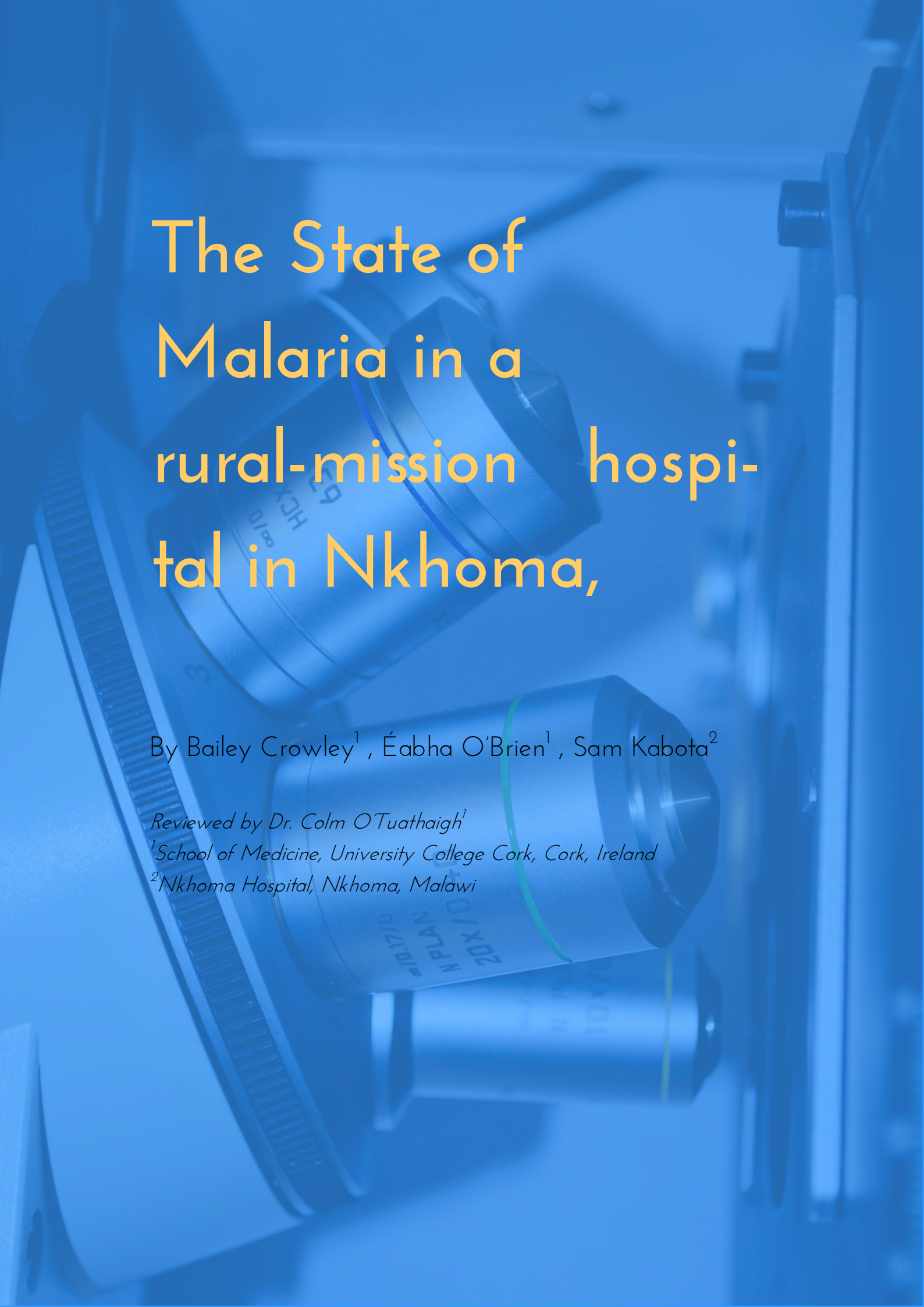
Table Of Contents

Page

Review Articles

Ethical Discussion

Elective Experiences



The State of Malaria in a rural-mission hospital in Nkhoma,

By Bailey Crowley[1] , Éabha O'Brien[1] , Sam Kabota[2]

Reviewed by Dr. Colm O'Tuathaigh[1]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]Nkhoma Hospital, Nkhoma, Malawi

Abstract

Title

The State of Malaria in a rural-mission hospital in Nkhoma, Malawi

Introduction

In recent times, Malaria has fallen out of the limelight due to an economical migration of populations into medium and higher income settings. Despite this, it remains endemic in 31 countries with 228 million cases per annum. In Malawi, the WHO have reported that all of its citizens are at risk of contracting the disease. In this study we hope to expand on the clinical data available at a rural mission hospital in Malawi, as well as highlight some of the external global health factors in such environments.

Methods

An observational retrospective cohort Study looking at severe malaria admission in a paediatric population was conducted. The Nkhoma hospital Paediatric department was the centre of the data collection which focused on the diagnosis of severe malaria, as well as the signs and symptoms and treatment regimens of same.

Results

Severe Malaria accounted for over 40% of all paediatric admissions in the month of May 2019. Patients suffered from anaemia (80%) and cerebral Malaria (41%), as well as a host of generalised symptoms such as fever (95%), vomiting (36%), malaise (30%), and diarrhoea (21%). Promisingly, a strict and comprehensive treatment regime for severe Malaria was in practice with artesunate, Lumefantrine used in ~100% of cases.

Conclusion

Sadly, Malaria continues to create horrendous amounts of morbidity and mortality, but our united commitment to eradicating Malaria is stronger than ever.

Introduction

Malaria has fallen out of the limelight due to an economical migration of populations into medium and higher income settings [1]. It is a communicable disease transmitted by Plasmodium in female mosquitos. Its clinical features include fever, anaemia, jaundice, hepatosplenomegaly, decreased consciousness, convulsions, renal failure, and acidosis. If left untreated, it has a mortality of approximately 100% [2]. Unfortunately, in 2019 Malaria remains endemic in 31 countries with 228 million cases per annum, of which over >90% of which are concentrated in sub-Saharan Africa [3] . While 2.7 billion United States dollars has been put forward by governments and organisations towards the global Malaria fund, this level of fiscal aid will not meet the milestones set by the Global technical strategy for Malaria 2016–2030 [4] . In Malawi, positive strides have been taken by centres such as The International Centers of Excellence for Malaria Research and the Malawi Ministry of Health in an effort to combat Malaria. These include an increase in suspected patient testing from 20% in 2010 to >95% in 2018, and the commencement of indoor residual spray (IRS) use [5] . Moreover, the last 10 years has seen a doubling in patients receiving internationally recommended treatment regimes in recognised healthcare facilities across the sub -Saharan African region. Nevertheless, much work remains unfinished with every citizen of the over 18 million people living in Malawi being classified as high risk for Malaria and less than 50% of those having access to a Long lasting insecticide net (LLIN) last night [3, 6] .

In this study we aim to expand the clinical data of Malaria in developing countries, and to explore the challenges faced by sub-Saharan African communities in combating this disease. We hope to do this by first providing a brief study looking at the classification, symptoms and treatments regimes of paediatric Malaria cases in a rural Presbyterian mission hospital in Nkhoma Malawi, and later providing commentary on both local and global health factors that play a role in healthcare.

Materials and Methods

Study Design

An observational retrospective cohort study was conducted looking at severe malaria admission in a paediatric population. This was facilitated by a research team consisting of two medical students and a paediatric clinical officer, in the department of paediatrics in Nkhoma hospital, Malawi. Appropriate cases were identified and relevant data were extracted from the charts of infants and children admitted during the month of May 2019. The following inclusion and exclusion criteria were utilised:

Inclusion:

- Age: ≤16
- Admitted date: May 2019
- Primary Admission Diagnosis: Severe Malaria

Exclusion:

- MRDT not performed, or the result unrecorded

Study Measures

1. Diagnosis of severe Malaria

   A positive MRDT plus with a minimum of one of the following:

   I. Anaemia
   II. The manifestations of cerebral Malaria
   III. Hyper-parasitaemia
   IV. Blackwater fever
   V. Electrolyte imbalance.

2. Signs & symptoms of severe Malaria:

   Specifically:
   I. Fever
   II. Malaise
   III. Vomiting
   IV. Diarrhoea
   V. Abdominal pain
   VI. Headache

3. Treatments of severe Malaria administered:

   Specifically:
   I. Artesunate
   II. Lumefantrine
   III. Paracetamol
   IV. Ferrous Fumarate
   V. Diazepam
   VI. Ceftriaxone
   VII. Blood Transfusion

Data Analysis

Descriptive data analysis was completed using Microsoft Excel V16.38. Clinical data was recorded using frequency and percentages.

Ethics

All data were collected and stored within Nkhoma Hospital paediatric department. No patient files were removed from the department and all data were anonymised as to not identify any participants. The nature of this study is exempt from ethical committee review. This is in keeping with the regulatory bodies of the Malawian Ministry of Health, the National Health Sciences Research Committee, the Malawi College of Medicine, and the Kamuzu College of Nursing.

Results

Classification of Malaria

During the month of May 2019, there were 253 admissions to the Nkhoma hospital paediatric unit. Within this there were 10 unused cases in the data. These cases charted the patient as having Malaria but no Malaria rapid diagnostic test (MRDT) was documented. In addition to this, there were 112 admissions of severe Malaria.

In this study, severe Malaria features were defined as anaemia, the manifestations of cerebral Malaria, hyper-parasitaemia, blackwater fever and electrolyte imbalance. Anaemia was the most common feature of severe Malaria with it being present in 89 admitted patients. Moreover, 27 of those cases had severe anaemia, a classification of haemoglobin levels of <6g/dL. Admissions with cerebral Malaria was the next largest group with 46, and an additional 1 admission had hyper-parasitaemia. There were no documented cases of either Blackwater fever or electrolyte imbalances. Finally, there were 5 cases where there was no charted documentation as to the reason for a severe Malaria diagnosis.

Table 1. Paediatric admissions.

Group	Admissions (n)	(%)
Total[1]	253	100
MRDT undocumented[2]	10	4
Severe Malaria	112	44

[1] *The Total group refers to all paediatric patients admitted regardless of diagnosis.*
[2] *The MRDT undocumented group refers specifically to the paediatric patients admitted without a MRDT mentioned in the patient notes.*

Symptoms of Malaria

Cases of severe Malaria noted six main symptoms. These included fever, vomiting, malaise, diarrhoea, abdominal pain, and headache. Fever was the most common symptom with it being resent in 106 of the 112 severe Malaria admissions. The next most common symptoms included: vomiting seen in 40 cases; malaise in 34 cases; diarrhoea in 23 cases, and abdominal pain in 9 cases. Headache was the least common symptom with only 7 admissions noting same.

Treatments of Malaria

A succinct group of medications were used in the treatment of severe Malaria. Artesunate, lumefantrine and paracetamol were staples to treatment with them being used in almost 100% of cases. Ceftriaxone was the next most common drug used with prescription at 69 cases. This was due to precautionary measures where cerebral Malaria and bacterial meningitis were unable to be distinguished clinically. Transfusions, ferrous fumarate and diazepam were some of the other drugs prescribed for anaemia for the former two options, and cerebral Malar-

Table 2. Distribution of Severe Malaria admissions.

Group	Admissions (N = 112) (n)	(%)
Anaemia	89	80
Severe Anaemia[1]	27	24
Cerebral Malaria	46	41
Hyper-parasitaemia	1	1
Blackwater fever	0	0
Electrolyte Imbalance	0	0
Unspecified[2]	5	4

[1] The Severe anaemia group refers to any patient with severe Malaria with a haemoglobin level of <6 g/dL.

[2] The Unspecified group refers to a documented case of severe Malaria as per Nkhoma Hospital criteria.

ia for the latter.

Discussion

Severe Malaria accounted for over 40% of all paediatric admissions in the month of May 2019. Patients suffered from anaemia (80%) and cerebral Malaria (41%), as well as a host of generalised symptoms such as fever (95%), vomiting (36%), malaise (30%), and diarrhoea (21%). Promisingly, a strict and comprehensive treatment regime for severe Malaria was in practice with artesunate, Lumefantrine used in ~100% of cases.

Table 3. Symptoms of Severe Malaria admissions.

Group	Admissions (N = 112) (n)	(%)
Fever	106	95
Vomiting	40	36
Malaise	34	30
Diarrhoea	23	21
Abdominal Pain	9	8
Headache	7	6

Classification of Malaria

Disease seasonal variation, management of non-severe cases, and criteria for severe diagnosis provide much insight into the significance of the results. It is well established that Malaria epidemiology contains a notable seasonal shift. In some countries, a seasonal Malaria chemoprevention (SMC) programme has been commenced to help deal with the issue [3] . Anecdotal evidence from the Nkhoma hospital claim that the dry season of April - September demonstrate the fewest number of cases of Malaria. With their almost 100 bed paediatric unit being nearly overrun in the wet season. Despite this, Malaria still accounted for 44% of all hospital admissions in the month of May 2019. Moreover, Hospital policy and healthcare guidance dictates that non-severe Malaria can be effectively treated as an outpatient [7] . This further emphasises the scale of Malaria cases that present overall. Further exploration of this statistic would be most beneficial in understanding the problem of Malaria in the community. Finally, this study had considerable differences in how severe Malaria was diagnosed. Guidance was taken using the WHO Malaria treatment guidelines 2015, oxford handbook of clinical medicine second edition [2, 7] . However, the definitive diagnosed was made by the paediatric clinical officers at the hospital, whose clinical decision was based off the inclusion of any of the criteria seen in table 2.

Table 4. Medications used in treatment of Severe Malaria admissions.

Group	Admissions (N = 112) (n)	(%)
Artesunate	112	100
Lumefantrine	111	99
Paracetamol	111	99
Ceftriaxone	69	62
Transfusion	38	34
Ferrous Fumarate	25	22
Diazepam	10	9

Symptoms of Severe Malaria

The symptom profile of severe Malaria in this setting provides important information to further enhance diagnosis. In particular, the near universal presentation of fever and the wide variety of generalised symptoms are of note. Fever was present in 106 of the 122 severe Malaria admissions. Therefore fever as a symptom was present in 95% of severe Malaria cases, and moreover in 40% of all admissions during the same timeframe. Modern developed hospitals' PEWS systems do not distinguish any serious clinical significance for fever [8] . Such a development, where Malaria is endemic, may lead to less than favourable patient outcomes. In addition to this, the remaining symptoms of vomiting, malaise, diarrhoea, abdominal pain and headache create diversity in presenting cases. There is a wide scope of variation within the symptom profile of Malaria. Therefore caution must be taken not to rule out Malaria. This is accounted for by the use of the MRDT, which is now used by over 80% of healthcare centres in the African region [3]

Treatment of Malaria

The committed adherence to treatment guidelines, despite the harshness of the disease rings loud. We see the implementation of Artesunate, Lumefantrine as staples in the treatment of all cases of Malaria [7] . It is admirable to see this trust by research centres out of their control given the despair seen with the disease. This is best seen with not only the levels of anaemia, but stark numbers of severe anaemia present in the population. Nevertheless, while understandable, its saddening to see the over prescription of antibiotics in the form of ceftriaxone. This has been employed in the hospital as not to miss any cases of bacterial meningitis, given the oftentimes striking clinical similarity between same and cerebral Malaria. These unfortunate developments have led to accelerated rates of antimicrobial resistance [9].

Malawi, Nkhoma, and Nkhoma Hospital

To better understand the significance of these results, we must apply them to the healthcare systems they affect. This will be examined by focusing on Malawi as a nation, the village of Nkhoma, and in particular its long established mission hospital.

Malawi

Malawi's economic and political landscape create a harsh environment for success. Located in sub-Saharan Africa, and bordered by its neighbour nations of Mozambique, Tanzania, and Zambia, Malawi is home to some of the poorest people in the world. Their GDP per capita (PPP) being consistently in the bottom ten of all countries worldwide [10] , with majority of its population living in extreme poverty, with >95% surviving on <5 USD daily [11] . In addition to this, Malawi has been victim to numerous scandals in government with international intervention needed to aid the democratic process. These have included "tip-ex" ballot tampering, presidential annulments, and the Democratic political party food rations scandal [12-14] . This degree of financial and administrative turmoil creates untold uncertainty across any nation. Despite this, however, Malawi still holds the titles of the warm heart of Africa by many internationally for the amicable behaviours of its people.

Nkhoma

Nkhoma village is best described through its religious, communal, and economic influences. At its core Nkhoma is a Presbyterian mission village with its synod having created a bright environment for its members to flourish [15] . Nkhoma is well known throughout Malawi for its opportunities in education with multiple primary schools as well as a third level institution with nursing and theology departments among others . Unfortunately however, Nkhoma's monetary divided position leaves much to be desired. In the grand scheme of things, Nkhoma is a wealthy Malawian village. But a clear financial split is seen throughout its citizens, and local businesses. In one circumstance numerous villagers live in well decorated red brick buildings, and use their own cars for transportation. These same people have the

privilege of working in the mission hospital or the large charity Peanut Butter and Jesus [16] . At the other extreme, people are living in straw-roofed huts or on the side of the road, and make ends meet by selling their produce or craft at the local bi-weekly market. Nevertheless, there is a proud sense of community in Nkhoma. There are plenty of sports facilitates which the locals use to full effect. These include association football, volleyball and squash, and are accessible to all ages and backgrounds. This commitment to community is also apparent at the dusk of nightfall with volunteers giving their time to patrol the area given historical thievery.

Nkhoma hospital

Nkhoma hospital is the pride of the village with its robust funding model, an extensive list of specialties, and international recognition [17] . Hospital Income is divided into roughly three equal parts of private donations, private patients, and government funding. This broad financial platform creates certainty for staff and patients as together a fall in one income source shouldn't discourage patient care. Furthermore, Nkhoma hospital boasts an impressive spectrum of facilitates. Its medical wards has TB isolation units, its Surgical wards have a specialised burns assembly, its Paediatrics department have the capacity for 100 in patients as well as a neonatal ward, It has a world class HIV unit, its OPD provides care for 200 patients a day, and its outreach clinic gives vaccinations to children from neighbouring towns. Additionally, Nkhoma has garnered international respect. Not only do patients come from hundreds of kilometres away to seek healthcare, and expected mothers sleep at the hospital's doorstep to have access to a safe birth. But organisations such as MSF have used Nkhoma hospital's palliative care department as a template for their own endeavours in the field [18] ; world renowned institutions such as the university of Edinburgh have partnered with the hospital for research purposes [18] , and the WHO have granted them access to be one the distributors of the trial Malaria vaccine RTS,S [19] .

Limitations and Future Studies

This study is naturally flawed due to its structure, its lack of mortality statistics, and its limited demographic detail. The study consisted of an external pair of retrospective data collectors succeeded by data analysis and global health commentary. It therefore contains inherent paucity in communicating with health professions who cared for the patients in the study. Moreover, due to hospital policy there is limited access to retrospective charts regarding levels of mortality. This creates a skewed view of the data presented, but perhaps illustrates the frightening reality of Malaria as only discharged patients were recorded in the study. Finally, there is a notable absence of a rich exploration into the demographics of the patients. This decision was largely based as a time constraints coupled with the sparse data collection equipment made available for the study.

Nkhoma Hospital's engagement in research provides much hope for future studies. Other endeavours in Malaria studies that may provide great insight include an inquiry into seasonal variation, as well as detailed comparisons across other healthcare centres. Such studies would put central in understanding the disease and further put patient care at the core of the research.

Conclusions

This study has been successful in expanding the clinical data of Malaria in the developing world, and in providing insight into the local and global health factors at play. This was done by examining the classification of Malaria, understanding the symptoms of the disease, and recognising extent and logic of the treatment regimes. To further comprehend this we provided a brisk overview of some of the external yet integral factors for health including political, economic and international unity. Sadly, Malaria continues to create horrendous amounts of morbidity and mortality, but our united commitment to eradicating Malaria is stronger than ever.

Acknowledgements

Bailey Crowley

At the time of research Dr. Crowley was a medical student at University College Cork on an Elective at Nkhoma Hospital. He was one of the two key data collectors. Almost one year after the data collection he decided to organise the scripture of the project and was one of the main contributors to the paper.

Éabha O'Brien

Dr. O'Brien was another medical student at the same mission hospital. She was the other key data collector and was instrumental in safe keeping of the data. Dr. O'Brien also played an important role in writing the project.

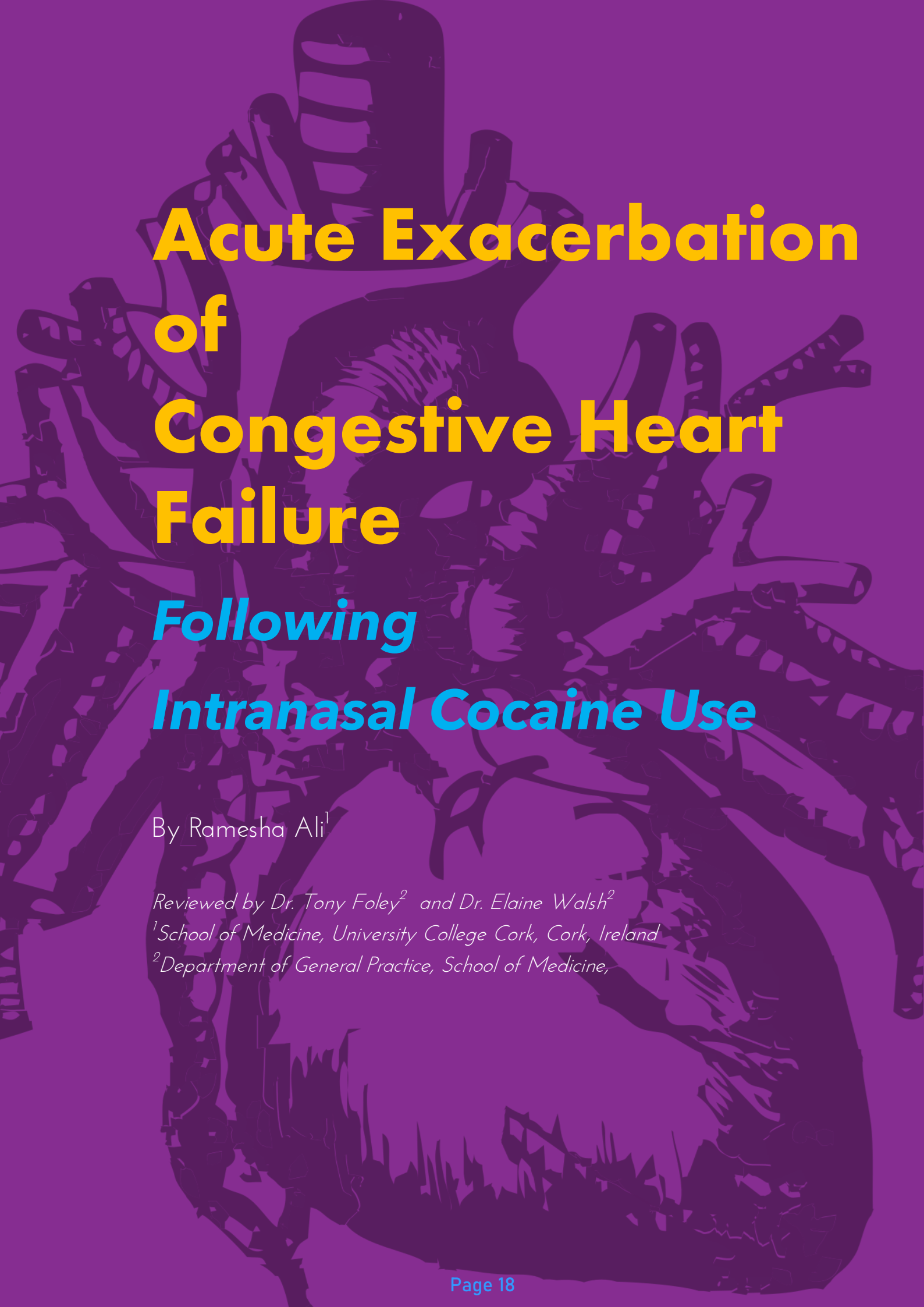
Sam Kabota

Sam Kabota is the paediatric clinical officer at Nkhoma Hospital. As principal investigator of the project, he provided guidance and support across the study.

References

1. Talapko J, Škrlec I, Alebić T, Jukić M, Včev A. Malaria: The Past and the Present. Microorganisms. 2019;7(6):179.
2. Longmore M, Wilkinson I, Baldwin A, Wallin E. Oxford Handbook of Clinical Medicine: Oxford University Press; 2014 2014-01.
3. Organization WH. World malaria report 2019. Geneva; 2019.
4. Orginisation WH. The global technical Strategy for Malaria 2016-2030. Geneva; 2015.
5. Mathanga DP, Walker ED, Wilson ML, Ali D, Taylor TE, Laufer MK. Malaria control in Malawi: current status and directions for the future. Acta Trop. 2012;121(3):212-7.
6. Programme TDaHS. Stat Complier - DHS 2017 [Available from: https://www.statcompiler.com/en/.
7. Orginisation WH. Guidelines for the treatment of Malaria. Third ed. G neva: WHO; 2015.
8. Health IDo. National Clinical Guidelines 2019 [Available from: https://www.gov.ie/en/collection/c9fa9a national-clinical-guidelines/.
9. Musicha P, Cornick JE, Bar-Zeev N, French N, Masesa C, Denis B, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study. The Lancet Infectious Diseases. 2017;17 (10):1042-52.
10. Fund IM. World Economic Outlook - GDP per capita. 2019.
11. Bank W. Poverty headcount ratio at $1.90 a day (2011 PPP) (% of population). 2011.
12. Henry Kijimwana Mhango AP-M. Malawi's 'Tipp-Ex' president set to appeal ruling that found his May election win was unlawful. The Telegraph. 2020.
13. BBC. Malawi's President Mutharika and the police food scandal 2018 [Available from: https://www.bbc.com/news/world-africa-44714224
14. Harding A. Malawi election: What the annulment means for democracy across Africa: BBC; 2020 [Available from: https://www.bbc.com/news/world-africa-51369191
15. Churches WCOr. Members 2020 [Available from: http://wcrc.ch/members
16. Inc. PBaJ. Peanut Butter and Jesus Inc.: Peanut Butter and Jesus Inc.; 2020 [Available from: http://pbjfoods.org/.
17. Hospital N. Nkhoma Mission Hospital Strategic Plan 2019-2022. 2019.
18. Scotland Go. Scottish Government Malawi Development Programme. University Of Edinburgh; 2019.
19. Malaria vaccine pilot launched in Malawi [press release]. geneva, 23rd of April 2019.

[This page has been intentionally left blank. Please turn over.]



Acute Exacerbation of Congestive Heart Failure

Following Intranasal Cocaine Use

By Ramesha Ali[1]

Reviewed by Dr. Tony Foley[2] and Dr. Elaine Walsh[2]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]Department of General Practice, School of Medicine,

Abstract

Background

Most presentations of decompensated congestive heart failure occur in patients diagnosed with pre-existing heart failure. Decompensation presents as progressive dyspnea, abdominal and peripheral congestion, as well as neurologic symptoms. It typically occurs following physiologic stressors such as infection, arrythmia, or medical non-adherence. Chronic heart failure may result from cardiovascular comorbid conditions, such as coronary artery disease, valvular disease, and long-standing hypertension.

Long term cocaine use also results in adverse cardiovascular health. Cocaine use can augment pre-existing risk factors for both chronic congestive heart failure and acute decompensations – namely, coronary artery disease, congestive heart failure, and peripheral vascular disease. It can also independently pose a cardiovascular risk by causing acute ischemia, vasoconstriction, tachycardia, systolic dysfunction, and cardiac remodelling.

The Case

The case of a 49-year-old Caucasian male who presented with worsening dyspnea on exertion and bilateral peripheral edema extending to his abdomen. His symptoms worsened over the preceding week and began after three consecutive days of intranasal cocaine use. He presented with a background history of congestive heart failure, coronary artery disease, peripheral vascular disease, a 30 pack-year smoking history, and weekly cocaine use for the past 12 years.

Conclusion

Cocaine use can lead to decompensation of congestive heart failure in patients with extensive cardiac and vascular disease. Cocaine use can also acutely worsen systolic function and cause demand ischemia, on a background of chronic remodelling and atherosclerotic changes.

Patient Consent Obtained

Yes.

Case Background

Decompensated heart failure may be the initial presentation of congestive heart failure (CHF) or a sign of worsening pre-existing and diagnosed heart failure. Development and severity of symptoms depend on the extent of underlying cardiac disease, as well as factors that may lead to acute worsening of symptoms. Nearly 70% of patients are admitted following an acute exacerbation and present with an acute-on-chronic heart failure episode[1]. Chronic heart failure may result from coronary artery disease, valvular disease, and poorly controlled hypertension. In the event of decompensated heart failure, precipitating factors such as infection, arrythmia, medical non-adherence, and uncontrolled hypertension, may be present [1]. Decompensation presents as progressive dyspnoea, abdominal and peripheral congestion, as well as neurologic symptoms.

Cocaine use is implicated in both chronic heart failure and decompensation with acute worsening of symptoms. Although it is not extensively identified as an acute precipitant of heart failure, it can worsen hypertension and lead to tachycardia, increasing myocardial oxygen demand while reducing oxygen supply through vasoconstriction [2]. It can also increase ventricular chamber size and cause systolic dysfunction, aiding in the pathogenesis of chronic cardiomyopathy. Cocaine use can induce fatal outcomes such as arrythmias and myocardial infarction [2]. By aiding in long-term cardiac remodelling and augmenting the risk factors for decompensation, it directly and indirectly worsens the prognoses of CHF and may contribute to an exacerbation. Additionally, cocaine can independently increase the risk of heart failure and systolic dysfunction, resulting in a poor cardiovascular health profile [2]. Previous literature has explored how long term cocaine use can lead to heart failure over time, however, an immediate and temporal association between cocaine use and decompensation has not been well documented.

Both cardiovascular mortality and all-cause mortality continue to be higher in cocaine users when compared to non-cocaine users. Cocaine users have two times the risk of sudden cardiac death compared to non-cocaine users alone [2]. The burden of cocaine on the healthcare system expands beyond its implications on heart disease, to further include the effects of chronic malnutrition often seen in cocaine users, due to its disruption of metabolic and neuroendocrine regulation [2].

This case report presents a 49-year-old Caucasian male who attended the emergency department with signs of decompensated CHF following intranasal cocaine use.

Case Details

A 49-year-old Caucasian male presented to the emergency department with worsening dyspnoea on exertion, lower extremity swelling extending to the abdomen, and lower extremity discomfort that started one week ago, following three consecutive days of intranasal cocaine use, approximately 80mg in total. The dyspnoea made him unable to carry out his activities of daily living and was relieved only by rest. Over the last week, his lower extremity swelling and abdominal distension gradually worsened, and he gained approximately three kilograms over the ten days preceding his admission.

He also experienced acute-on-chronic bilateral leg discomfort with erythema, eschar formation, and venous ulcers above the medial malleoli bilaterally. The lower extremity erythema and eschar formation, over both tibias, had been present for the past year. However, over the past week, he experienced increased skin breakdown with superficial wounds, areas of slough and serosanguinous discharge from both lower legs. He described his leg discomfort as diffuse, 10/10 in severity, rendering him unable to ambulate.

Systemically, he experienced generalized fatigue but no fever, chills, or sweats. He denied orthopnea, paroxysmal nocturnal dyspnoea, cough, recent illness, or any insult to his lower extremities.

He presented on a background history of congestive heart failure, coronary artery disease, peripheral vascular disease, 30 pack-year smoking history, and weekly cocaine use, approximately 15mg each week for the past 12 years. His past medical history was significant for dyslipidemia and three ST-elevation myocardial infarctions (STEMI MI), all requiring percutaneous coronary intervention (PCI). His medications included aspirin, metoprolol, ramipril, and spironolactone, to which he was adherent. Family history was significant for his father who passed away from a MI. Social history was significant for social housing in a low- income area associated with significant cocaine use among the residents, as well as the previously noted substance abuse. The patient also consumed approximately 10-12 units of alcohol per week, predominantly on the weekends.

On examination, the patient was unable to comfortably position his legs, which were elevated and exposed. His jugular venous pressure was elevated to 2cm above the angle of the jaw. Auscultation of the lungs revealed bilateral crackles in the lower lobes. The abdomen was distended but non-tender. The liver and spleen edge could not be ascertained due to the ascites and distension. Shifting dullness and fluid thrill were present. On peripheral examination, the patient had significant bilateral erythema and eschar formation, particularly inferior to the knee, and the right lower extremity was worse than the left. Extensive skin breakdown resulted in wounds that were draining serosanguinous fluid. There were ulcers above both medial malleoli, approximately 7cm in diameter each, with exudate. The temperature was warm and equal in both lower extremities, with tenderness to palpation bilaterally. Pitting oedema extended to the abdomen and was characterized as 4+. The dorsalis pedis and posterior tibialis pulses could not be palpated bilaterally. The patient's vital signs were within normal ranges. At this time, differential diagnoses included both decompensated liver failure as well as decompensated congestive heart failure.

Investigations

Laboratory investigation revealed hyponatremia (119 mmol/L), elevated troponin (0.039 mg/L), elevated gamma glutamyl transferase (GGT) (383 U/L) and an elevated C-reactive protein (8.4 mg/L). The patient also had lactic acidosis with lactate levels elevated at 2.6 mmol/L. The patient's GGT level was similar to that reported during his previous admission in 2017. However, remaining laboratory derangements were new or worsened.

An echocardiogram revealed a left ventricular (LV) ejection fraction of 18% with moderate right ventricular (RV) hypertrophy and moderate tricuspid regurgitation and dysfunction. A CT angiogram of the abdomen, pelvis, and lower extremities revealed significant burden of atherosclerotic disease, and a doppler ultrasound also revealed worsened peripheral vascular disease compared to a study performed in 2017. A chest x-ray revealed borderline enlargement of the pericardial silhouette with mild pulmonary oedema in the lower lobes and notable atelectasis. A wound culture confirmed colonization of venous ulcers with Pseudomonas aeruginosa. An ultrasound of the abdomen revelated an enlarged liver by 6-7cm and gallbladder wall thickening, secondary to ascites.

Following these investigations, the diagnoses was confirmed to be decompensated congestive heart failure, New York Heart Association (NYHA) Class III.

Management:

The patient was commenced on IV furosemide and Milrinone until he reached a euvolemic state, at which point he was transitioned to oral furosemide only. He was commenced on a low salt diet and fluid restriction with daily assessment of weight. A therapeutic ultrasound guided paracentesis was performed for ascites, and approximately four liters of fluid were removed. Troponin was slightly elevated secondary to demand ischaemia, as no ischemic changes were seen on ECG and necessitated no further workup. Wound care involved treatment with

both ceftazidime and vancomycin as well as adequate dressing and coverage.

Discussion

Heart failure continues to be a significant contributor to poor quality of life, healthcare burden, and admission times [1] Although many individuals do not experience an acute exacerbation following intranasal cocaine use, it can augment the risk posed by other risk factors and aid in an exacerbation. Persistent use of cocaine increases the risk of vascular disease as well as promotes cardiac remodelling, resulting in cardiomyopathy. Unfortunately, this patient's non-modifiable risk factors, namely age, sex, previous MI, and familial history place him at a higher risk of developing CHF, coronary artery disease (CAD), peripheral vascular disease (PVD), and associated complications [3]. In addition, modifiable risk factors such as smoking can independently double the risk of mortality and dyslipidema [3,4]. These risk factors can accelerate and increase the toxicity associated with cocaine use and cause increased deterioration of cardiovascular health.

This case demonstrates how a preceding poor cardiac function profile can accelerate progression to an acute CHF exacerbation. Specifically, an LV ejection fraction of 18% with moderate RV hypertrophy, and moderate tricuspid regurgitation and dysfunction, as seen in this patient, pose independent risks for CHF exacerbation [3]. Additionally, the use of cocaine can lead to the development of dilated cardiomyopathy due to deprived myocardial oxygen supply, ventricular hypertrophy, as well as decreased left ventricular contractility through blockage of sodium transport and norepinephrine uptake in the myocardium [3]. It can also promote platelet adherence and thrombosis, augmenting atherosclerotic disease burden. Therefore, cocaine use can be a toxic risk precipitant of both CHF exacerbations and vascular disease. Cocaine use is associated with complications such as MI and arrythmias and increases the risk of CHF by 5-7% [2,5]. Cocaine also promotes peripheral atherosclerosis, skin ischaemia , and deep vein thrombosis, which can further contribute to worsening ulcers, as seen in this patient [5]. Whereas much of the existing literature focuses on the long term effects of cocaine use, this case provides a unique example of an acute and immediate adverse effect of cocaine on a previously poor cardiovascular profile, as evidenced by the sudden decompensation experienced by this patient.

It is important to assess such risk factors to better manage long-term prognosis and mortality rate. Substance use alone poses significant risks and highlights the need for education as well as access to interventions and support. It is also important to understand how poor peripheral health may represent the cycle of ill health patients often experience, as oedema and skin breakdown can make it difficult to ambulate, which further increase the risk of developing venous ulcers, as in this patient. Attention to the psychological and social context to which this patient presents can aid in education and encouragement of cessation of substance abuse. Addressing many of this patient's comorbid conditions that are risk factors for decompensated CHF will help improve his wellbeing and prevent future exacerbations [6]. Practical recommendations may include coordination with social workers to help alleviate the social limitations experienced by this patient, such as late presentation due to accessibility concerns. Furthermore, motivational interviewing at bedside as well as frequent follow-up and support in both an inpatient and outpatient setting, respectively, can support this patient in cocaine cessation.

This patient had several comorbid conditions on presentation, and his progression throughout his admission also raised the concern of discontinuity of care – which independently increases the risk of prolonged and emergency admissions [7,8]. A CHF exacerbation may require care in both the cardiac care unit (CCU) and intensive care unit (ICU), as medications such as Milrinone require ICU supervision in some hos-

pitals. Patient transfers between the CCU to the ICU may lead to care provision by different physicians, as well as a change in allied health professional administered care, such as physiotherapists, occupational therapists, and social workers. Although these transitions are inevitable and performed in the best interest of the patient, each instance of discontinuity is associated with lower clinical condition scores and increased time to recovery, as assessed by the Rothman Index [7].

Conclusions

This case discusses a 49-year-old male who presented with decompensated CHF following intranasal cocaine, as well as PVD stigmata with superimposed bacterial infections. He had several modifiable and non-modifiable risk factors associated with worse cardiovascular health. Although a prior direct causal link has not been established between cocaine and acute CHF exacerbations, cocaine use can augment the deleterious effects of these risk factors in an acute setting. This case contributes to our understanding of how cocaine use can acutely lead to decompensated CHF on a background of poor cardiovascular health, secondary to chronic cocaine use.

References

1. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Reviews in cardiovascular medicine. 2003;4:S21-30.
2. Kim, S.T. and Park, T., 2019. Acute and chronic effects of cocaine on cardiovascular health. International journal of molecular sciences, 20(3), p.584.
3. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nature Reviews Cardiology. 2011 Jan;8(1):30.
4. Hajar R. Risk factors for coronary artery disease: historical perspectives. Heart views: the official journal of the Gulf Heart Association. 2017 Jul;18(3):109.
5. Kim ST, Park T. Acute and Chronic Effects of Cocaine on Cardiovascular Health. International journal of molecular sciences. 2019 Jan;20 (3):584.
6. Finlayson K, Wu ML, Edwards HE. Identifying risk factors and protective factors for venous leg ulcer recurrence using a theoretical approach: A longitudinal study. International journal of nursing studies. 2015 Jun 1;52(6):1042-51.
7. Yakusheva O, Costa DK, Weiss M. Patients negatively impacted by discontinuity of nursing care during acute hospitalization. Medical care. 2017 Apr 1;55(4):421-7.
8. Tammes P, Purdy S, Salisbury C, MacKichan F, Lasserson D, Morris RW. Continuity of primary care and emergency hospital admissions among older patients in England. The Annals of Family Medicine. 2017 Nov 1;15(6):515-22.

[This page has been intentionally left blank. Please turn over.]

Right Knee ACL, PCL, and MCL Reconstruction *with Sports-Related Anxiety*

By Avnee Nulkar[1], Dr. Kazi Najamus-Saqib Khan[2]

Reviewed by Dr. Colin Bradley[3] and Dr. Henry Smithson[3]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]South Infirmary Victoria University Hospital, Cork, Ireland
[3]Department of General Practice, School of Medicine, University College Cork, Cork, Ireland

Abstract

Introduction

JM, a 20-year-old male professional ice hockey player, presented with a 2-week history of lack of range of motion, weakness, and pain in his right knee, after a 2-year post-medial collateral ligament repair of the right knee and 3 year-post anterior cruciate ligament, posterior cruciate ligament, and medial collateral ligament reconstruction of the right knee.

Case Description

In the course of history taking, it was revealed that 5 months prior to admission the patient had been informed by a psychiatrist that he had sport-related anxiety. With an unremarkable psychiatric history prior to age 18, the competitive nature of his sports career in addition to financial pressures may have contributed to his sports-related anxiety. His examination findings were consistent with a diagnosis of complete tears of the right anterior cruciate ligament and posterior cruciate ligament along with a grade III medial collateral ligament injury.

Discussion

The biopsychosocial model was used to explicate JM's case. JM's current injuries prompted reconstruction of the anterior cruciate, posterior cruciate, and medical collateral ligaments. Psychologically, JM's sports-related anxiety is not a rare phenomenon as recent studies have discovered an increased risk of sports-related anxiety amongst young professional athletes. Sports-related anxiety, along with competitive trait anxiety, may be factors that contribute to sports injury occurrence. Other psychosocial stressors can add to sports-related or competitive trait anxiety, further increasing the risk of sports injury reoccurrence.

Summary

JM was admitted for a right knee open medial collateral ligament repair with internal bracing, anterior cruciate ligament reconstruction, posterior cruciate ligament reconstruction, and platelet rich plasma injection. As part of a holistic patient-centered treatment plan, a referral to psychiatry was made to address JM's sports-related anxiety with the goal of decreasing future risk of sports injury.

Patient's Consent Obtained

Yes.

Introduction

Patient Details

Name: JM
Dates Seen: October 28-November 1, 2019
Location: USA

Glossary of Abbreviations

ACL: anterior cruciate ligament
ARecon: arthroscopic reconstruction
ARep: arthroscopic repair
AVPU: alert, verbal, pain, unresponsive
BMI: body mass index
CBT: cognitive behavioral therapy
CTA: competitive trait anxiety
CVS: cardiovascular
GI: gastrointestinal
Hx: history
ICE: ideas, concerns, expectations
LCL: lateral collateral ligament
MCL: medial collateral ligament
MLIs: multiple ligament injuries
MRI: magnetic resonance imaging
MSK: musculoskeletal
Neuro: neurological
NKDA: no known drug allergies
P/C: presenting complaint
PCL: posterior cruciate ligament
PRP: platelet rich plasma
PSSI: perceived susceptibility to sport injury
RCT: random controlled trial
Resp: respiratory
ROM: range of motion
ROS: review of systems
SI: sports injury
SIO: sports injury occurrence
SRA: sports-related anxiety

Case Description

Case History

JM is a 20-year-old male professional ice hockey player who presented with a 2-week history of lack of ROM, weakness, and pain in his right knee after a two-year post-MCL repair of the right knee and three-year post ACL, PCL, and MCL reconstruction of the right knee. JM re-injured his knee during a hockey game; JM was tackled and fell onto the ice with his right knee extended and laterally rotated. JM was conscious after the fall and remembers sharp pain in his right knee. The pain was localized to right medial and anterior knee and was rated as 6/10 after the initial fall. On exam, lack of range of motion was observed with flexion, extension, and rotation of the knee. He demonstrated an antalgic gait without use of crutches along with positive right knee anterior drawer, Lachman, posterior drawer, and valgus stress tests.
In the past, JM underwent ARecon of right ACL, PCL, and MCL (April 2016) and ARep of right MCL (July 2017). With an unremarkable medical and family history, JM began sessions with a psychiatrist in May 2019 due to nervous thoughts, excessive diaphoresis, and nausea before scrimmages. Although there was no DSM diagnosis, he was told he has SRA with ice hockey and was referred to Ph.D. psychologist for CBT. In familial context, JM gained control of his family's finances two years prior. JM had never been given endorsements, yet he helped pay his parents' mortgage. During JM's childhood, his family spent funds on his ice hockey career. JM has since felt financially responsible for his family. JM has never drunk nor smoked and describes himself as well-liked, liberal-minded, adaptable, athletic, and easy-going. He hopes to feel "ready to play" as soon as possible and acknowledged that health and recovery time were important for long-term results. His main concern involved his time of return to play and its impact on his family's finances.

Diagnosis & Treatment Plan

MRI results included a non-visualization of ACL and PCL fibers indicative of complete full thickness tears as well as a grade III MCL injury. A surgical plan involving right knee open MCL repair with internal bracing, ACL reconstruction, PCL reconstruction, and PRP injection was planned.

Discussion

To explicate this case, the biopsychosocial model will be used. Developed by George Engel, this model is an application of general systems theory to humanity [1]. Although studies acknowledge the difficulty of implementing this model across all cases, each patient's biopsychosocial circumstance should be considered in a multidisciplinary, patient-centered approach [1,2]. The medical team responsible for patient care should therefore address the biological disease, social context of the patient's life, and the patient's psychological position to create a holistic, patient-centered treatment plan.

Biological Factors

In professional sports, MLIs can involve at least 2 of 4 ligaments – the ACL, PCL, MCL, or LCL. Although individual ligament injuries prompt standardized treatments, less consensus regarding treatment of MLIs exists; therefore, research assessing treatments and success rates of MLIs has been conducted recently. In fact, early operative intervention of MLIs, compared to rehabilitation and time, is associated with increased functional and clinical outcomes [3]. Now, researchers have proposed a "standard" treat-

ment for MLIs. A thorough physical exam should include Lachman's test, Posterior Drawer test, valgus stress at 0 and 30 degrees of flexion, varus stress at 30 degrees flexion, Slocum test, and External Rotation Dial test [3]. A stress radiography to visualize functional laxities can also supplement the MRI.

Once in the operating room, the medical team should prepare reconstructive grafts. A patellar tendon is the PCL graft choice, ipsilateral hamstring (gracilis or semitendinosus) is for the ACL, and semitendinosus allografts are used for the MCL and LCL [3,4]. Due to JM's athleticism, his first ACL reconstruction was a patellar tendon, and this second reconstruction called for a hamstring graft. Although autografts may result in speedier recovery times in athletes, RCTs have discovered no significant differences result in speedier recovery times in athletes, RCTs have discovered no significant differences

Psychological Factors

In April 2019, JM experienced anxious thoughts, excessive diaphoresis, and nausea the morning of a practice game. He had experienced nervousness and nausea before games, but the accompanied diaphoresis and focus on intrusive thoughts began in January 2019. He therefore visited a psychiatrist, who disclosed JM's SRA.

Although not a DSM diagnosis, SRA is broadly defined as a trait and/or state-like response to a stressful sports circumstance, in which the patient experiences cognitive appraisals, physiological arousal, and/or behavioral reactions [5]. A patient's poor response to a stressful sports-related circumstance is associated with an increased risk of SI [6,7]. In addition to impacting SI onset, anxiety and poor coping mechanisms can affect physical and psychosocial rehabilitation results [6,7].

For JM, his age correlates with that of a meta-analysis finding – competitive elite competition directly overlaps with peak ages of mental disorder onset. 75% of mental disorders typically occur before age 25, with elite athletes feeling discouraged from disclosing their anxiety due to stigma and fear of not making team selection.[6,7] JM's role as an alternate also demonstrates that elite athletes at higher competitive levels report fewer levels of anxiety, compared to their second-string counterparts [7].

In January 2019, JM graduated from benched player to alternate, one rung below first-string. The possibility of replacing an injured first-string player may have triggered his SRA, even during practice games. Although the mechanism of anxiety leading to injury is unclear, this SRA may have been a factor in JM's reinjury of his right ACL, PCL, and MCL. To combat re-injury and further anxiety, JM was referred to a sports-specialized psychiatrist after his surgery and a sports-specific rehabilitation center.

Social Factors

Although JM's anxiety appears to originate from sports, his financial stress may have contributed to his current state. During the economic recession, his parents lost more than half of their savings. They then relied on food stamps and moved to affordable housing, an hour and a half away from the closest ice rink. What was left of their finances was sent to JM for his hopeful ice hockey career.

Now, JM feels responsible for his family's finances. Financial strain at a young age is correlated with physical health problems during adulthood [8]. On the other hand, acute periods of strain are more likely linked with mental health changes, compared to physical ones [8,9]. In athletes, excessive stress increases the risk of injury and even acute illness onset [10]. In fact, multiple research studies in the 2000s and 2010s discovered that sports injuries in elite athletes are the accumulated result of physical and psychosocial stressors [10]. In addition to JM's game-related stress, the financial burden may have worsened his anxiety and contributed to his re-injury. To complete a holistic treatment plan, JM should also been spoken to about the financial burden in and the possibility in referring to a financial advisor or group therapist in the matters of his family's economic situation.

Sports-Related Anxiety and Sports Injuries

Approximately 3 to 7 million sports-related injuries arise in the US each year [11]. Accompanying these injuries are physical pain, fear of injury, and psychological impacts. One psychological phenomenon, informally termed SRA, has been explained through numerous models, with the following holding true: SRA affects performance; the effect on performance can be negative or positive, depending on the individual and context; the nature of the effect is a product of the individual's physiological, behavioral, and cognitive responses to the stressful sport context [11].

Although SRA is relatively novel topic, factors that lead to this kind of anxiety have major implications. More specifically, factors or stressors that lead to the development of SRA may contribute to sports-related injuries [11]. These factors include the intensity of sport, intensity of stressors, and athlete's personality, history, and coping mechanisms. An athlete's poor stress response to a situation increases his risk of SI, with anxiety itself being an athlete's personality trait that can lead to SI [11,12]. A 2017 critically appraised topic review concluded that 66% of studies found results supporting CTA – the tendency to experience stress in competitive sports contexts - as the most consistent factor associated with SIO [12]. Although CTA and SRA are different terms, multiple studies use them interchangeably. Interestingly, CTA can predict SIO only when considered in tandem with other psychosocial factors like worry, life stressors, and the efficacy of one's coping skills. Assessed alone, CTA does not have predictive value for SIO. Researchers attribute this finding to the multidimensional essence of the relationship between SIO and SRA.

In addition to competitive trait anxiety, PSSI has been proposed as a potential influencer of SIO. A prospective study conducted in the early 2000s with 434 hockey, soccer, and football players discovered that an athlete's PSSI, or fear of injury, increases the risk of SIO [13]. Later studies then revealed that PSSI is linked to neuroticism, which is closely associated with trait anxiety [14-17]. CTA, SRA, and PSSI are fairly novel terms, and further studies are needed to bolster the connections found between them and SIO.

Conclusion

In terms of JM's case, JM himself explained his unofficial SRA diagnosis by a psychologist and his own level of stress, concern, and worry regarding his responsibility for family finances. Paralleling past studies' findings, the combination of JM's SRA or CTA, stress levels, and ongoing worry may have contributed to his multiple, recurring sports injuries involving his MCL, ACL, and PCL. Although a causal relationship cannot be determined, his SRA and psychosocial stressors most likely increased his risk for SIO.

Summary

This case concerns a patient admitted for lack of ROM, weakness, and pain in his right knee due to a professional ice hockey injury. During his time in hospital, JM revealed invasive, anxious thoughts since graduating to an alternate player from a benched one. The surgeon admitted JM for a right knee open MCL repair with internal bracing, ACL and PCL reconstructions, and PRP injection. However, the possibility of JM's SRA playing a role in his susceptibility to injury during early season could not be ruled out. Past research detailing the connections between competitive trait or SRA and SIO provided further reasons for a psychiatric referral. The recommendation of a psychiatrist who specializes in athletic performance anxiety was made, in addition to a prescription for 6 to 12 weeks of sports rehabilitation.

References

1. Kusnanto H, Agustian D, Hilmanto D. Biopsychosocial model of illnesses in primary care: A hermeneutic literature review. Journal of Family Medicine and Primary Care. 2018;7(3):497.
2. Wade D, Halligan P. The biopsychosocial model of illness: a model whose time has come. Clinical Rehabilitation. 2017;31(8):995-1004.
3. Buyukdogan K, Laidlaw M, Miller M. Surgical Management of the Multiple-Ligament Knee Injury. Arthroscopy Techniques. 2018;7(2):e147-e164.
4. Mistry H, Metcalfe A, Colquitt J, Loveman E, Smith N, Royle P et al. Autograft or allograft for reconstruction of anterior cruciate ligament: a health economics perspective. Knee Surgery, Sports Traumatology, Arthroscopy. 2019;27(6):1782-1790.
5. Macaulay A, Perfetti D, Levine W. Anterior Cruciate Ligament Graft Choices. Sports Health: A Multidisciplinary Approach. 2011;4(1):63-68.
6. Ford J, Ildefonso K, Jones M, Arvinen-Barrow M. Sport-related anxiety: current insights. Open Access Journal of Sports Medicine. 2017;Volume 8:205-212.
7. Rice S, Gwyther K, Santesteban-Echarri O, Baron D, Gorczynski P, Gouttebarge V et al. Determinants of anxiety in elite athletes: a systematic review and meta-analysis. British Journal of Sports Medicine. 2019;53 (11):722-730.
8. Whitehead B, Bergeman C. The effect of the financial crisis on physical health: Perceived impact matters. Journal of Health Psychology. 2015;22(7):864-873
9. Prentice C, McKillop D, French D. How financial strain affects health: Evidence from the Dutch National Bank Household Survey. Social Science & Medicine. 2017;178:127-135.
10. Hamlin M, Wilkes D, Elliot C, Lizamore C, Kathiravel Y. Monitoring Training Loads and Perceived Stress in Young Elite University Athletes. Frontiers in Physiology. 2019;10.
11. Hsu C, Meierbachtol A, George S, Chmielewski T. Fear of reinjury in athletes: Implications for rehabilitation. Sports Health. 2017;9(2):162-167.
12. Cagle A, Overcash K, Rowe D, Needle A. Trait anxiety as a risk factor for musculoskeletal injury in athletes: a critically appraised topic. Int J Athl Train Ther. 2017;22 (3):26–31.
13. Reuter JM, Short SE. The relationships among three components of perceived risk of injury, previous injuries and gender in non-contact/limited contact sport athletes. Athl Insight Online J Sport Psychol. 2005;7 (1):20–42.
14. Deroche TS, Y, Brewer B, Le Scanff C. Predictors of perceived susceptibility to sport-related injury. Pers Individ Differences. 2007;43:2218–2228.
15. Deroche T, Stephan Y, Woodman T, Le Scanff C. Psychological mediators of the sport injury–perceived risk relationship. Risk Anal. 2012;31(1):113–121.
16. Stephan Y, Deroche T, Brewer B, Caudroit J, Le Scanff C. Predictors of perceived susceptibility to sport-related injury among competitive runners: the role of previous experience, neuroticism, and passion for running. Appl Psychol. 2009;58(4):672–687.
17. Binboga E, Guven S, Çatıkkaş F, Bayazıt O, Tok S. Psychophysiological responses to competition and the Big Five personality traits. J Hum Kinet. 2012;33:187–194.

The Effects of Postoperative Delirium on Outcomes in Hip Fracture Patients

By Kieran FitzGerald[1], Dr. Brian O'Donnell[2]

Reviewed by Dr. Colm O'Tuathaigh[1]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of Anaesthetics, Cork University Hospital,

Abstract

Background

Hip fractures have reached epidemic levels in an ever-ageing population. Based on this increase, the rate of postoperative delirium (POD) is simultaneously expected to rise as it seems to be a disproportionate hazard post-hip surgery. POD is purported to have detrimental effects, but prevention and screening efforts remain inadequate. Therefore, examination of recent evidence for negative outcomes, including decreased survival and increased complications, is critical if we seek best practice.

Objectives

This review examines the most recent evidence for the effect of POD on mortality of hip fracture patients and other outcomes such as length of stay, discharge destination and functional outcomes.

Methods

Two electronic databases searches resulted in selection and critical appraisal of ten studies.

Results

Across the ten articles selected for review, the prevalence of POD ranged from 18-53.3%. Nine studies focused on mortality. In unadjusted analysis, mortality was found to have a significantly increased association with POD. However, several papers showed with effective adjustment for confounding or contributory variables, no independent association was observed. Medical complications was a focus in four of the articles, and the association with POD was observed following adjustment. Similar results were reported for increased non-home discharge and length of hospital stay.

Conclusion

POD has some effect on outcomes in hip surgeries but future research needs coherence of methods across the field and comprehensive accounting for the increased age and comorbidities of POD patients. Determining whether factors like increased length of stay are themselves the cause, rather than the result, is imperative. The lack of consistent high-quality research frustrates the validity of many of the papers conclusions on increased mortality. While we await such research an effort still needs to be made to prevent POD, especially given the more valid evidence of other less fatal effects.

Introduction

Hip fractures have been termed a modern epidemic [1] as the second leading cause of hospitalization in the growing cohort of '65 years and older' [2]. In 2000 there were 1.6 million hip fractures worldwide, with predicted increase to 4.5–6.3 million by 2050 [3]. A hip fracture can be a fatal turning point. One-year mortality rate is reportedly 20–24%. It is shown that 40% were unable to walk independently, while 60% required assistance with activities of daily living [4]. This crisis is stretching healthcare costs and rehabilitation services. This is evident in Ireland, where from 2000 to 2014, there has been a 51% increase in bed days for osteoporotic fractures, and hip fractures making up 47% of those bed days [5].

There is growing understanding of the various perioperative factors that predict poorer outcomes and increased mortality post hip surgery. These include age, ASA score [6], time to surgery,[7] comorbidities, pre-fracture mobility[8], and cognitive impairment [9]. However, there is scope to further scrutinize and delve into perioperative variables, in order to guide advances in hip fracture management.

POD is defined as an 'acute brain dysfunction,' which shows similar symptoms to dementia, but is expected to improve when 'causative factors' are normalized [10]. It varies in severity and duration, and it has been noted specifically that symptoms may differ if POD co-exists with dementia [11]. Symptoms are screened for using diagnostic tools noting onset, course, inattention, disorganized thinking and consciousness.

There seems to be a disproportionate risk post hip surgery, with reported incidence up to 53.3% [12]. It is postulated that this is due to the increased age of hip patients and the 'threshold theory of cognitive decline' which describes the elderly as having a diminished brain reserve capacity, or on a 'functional cliff' for developing POD when experiencing a strain such as hip surgery [13].

This review aims to examine the reported effect POD can have, mainly on mortality, length of stay, and institutionalization – the most popular measured outcomes in the literature.

Glossary of Abbreviations

AOR: Adjusted Odds Ratio

ASA: American Society of Anesthesiologists

CAM: Confusion Assessment Method

CI: Confidence Interval

DOSS: Delirium Observation Screening Scale

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

FNF: Femoral neck fracture

HR: Hazard Ratio

IF: Internal Fixation

IQR: Interquartile Range

LOS: Length of Stay

MMSE: Mini Mental State Exam

NOF: Neck of Femur

OR: Odds Ratio

ORIF: Open rotation internal fixation

P: p-value

POD: Postoperative Delirium

THA: Total Hip Arthroplasty

Objectives

This systematic review aims to evaluate recent literature within the following objectives:

1. Examine the evidence for the effect of POD on mortality of hip fracture patients.
2. Determine the reported impact of POD on other outcomes such as length of stay, functionality, readmission.

Methods

On 20/01/2020, electronic database searches were undertaken using the following terms:

PubMed: All (Title/Abstract)

I. delirium or POD or cognitive dysfunction or cognitive impairment or POCD

II. postoperative or after surgery or post-op or post-surgery or surgical or after hip surgery

III. hip fracture or neck of femur or femoral neck or hip fracture or neck of femur fracture or femoral neck fracture or NOF fracture or proximal femur or fractured neck of femur

IV. outcomes or predictor or impact or mortality or indicator or sequelae or complications

EBSCO (MEDLINE)

I. (Abstract) delirium or POD or cognitive dysfunction or cognitive impairment or POCD

II. (Abstract) postoperative or after surgery or post-op or post-surgery or surgical or after hip surgery

III. (Abstract) hip fracture or neck of femur or femoral neck or hip fracture or neck of femur fracture or femoral neck fracture or nof fracture or proximal femur or fractured neck of femur

IV. (Title) outcomes or predictor or impact or mortality or indicator or sequelae or complications

Inclusion Criteria

- Published 2010-2020
- Evaluates hip fracture patients postoperatively
- Examines mortality or other outcomes postoperatively
- Includes POD as a variable

Exclusion Criteria

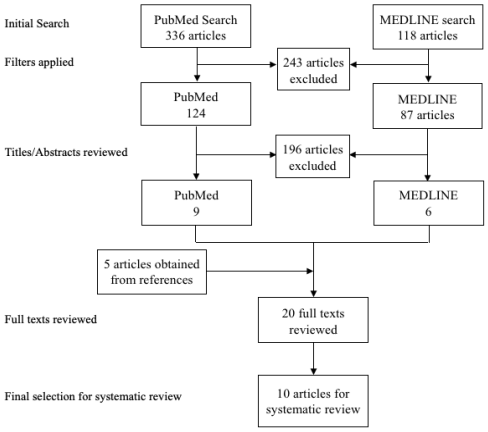
- No full text or English available
- Included knee fracture patients
- Focus on analgesia, anesthesia, or surgery
- Systematic reviews, meta-analyses, case studies

Selection Process

The initial search results and filter applications are shown in Figure 1. The remaining papers were reviewed by title and/or abstract to select the most relevant. Many were excluded by title alone due to obvious exclusion criteria breaches. The more appropriate articles were reviewed by abstract, until twenty full texts were examined, including five from references. Finally, ten articles were selected for systematic review.

After selection, the details of these papers were summarized using a table of results with the headings: Author, (Year) Location, Title, Study Design, Sample Size, Population, Key Findings, Strengths and Limitations. Critical appraisal for each article was by the EBL checklist, found in the appendix, and subsequent validity score, found in Table 1. This is a standardized checklist that determines study quality and validity using specific questions on sampling, data collection, results and design.

Figure 1
Selection process



Results

The prevalence of POD across the articles ranged from 18%-53%.

Mortality

Nine studies dealt with mortality, many giving results that backed an increased mortality rate with POD. Arshi et al. reported POD patients had a significantly higher risk-adjusted 30-day mortality (OR 2.22 [1.74-2.84]). [13] De Jong et al. stated POD was a significant predictor of 1-year mortality, remaining after multivariate analyses, (OR 1.93, P=0.016). [16] Choi et al described that All POD patients had significantly lower survival rates at 2-year follow-up than control (77.1% vs 87.8%; p<0.001). This study also reported that immediate POD had significantly lower survival (71.0%) than control

Table 1
Validation scoring based on EBL Critical Appraisal Checklist
Four of the studies were found to be invalid (< 75%).

Article	Population (%)	Data Collection (%)	Study Design (%)	Results (%)	Overall (%)
Arshi et al. (2018) Predictors and Sequelae of POD in Geriatric Hip Fracture Patients	66.7	50.0	80.0	83.3	67.8
Belleli et al (2014) Duration of POD Is an Independent Predictor of 6-Month Mortality in Older Adults After Hip Fracture	66.7	62.5	80.0	100.0	75.0
Choi et al. (2017) Early POD after hemiarthroplasty in elderly patients aged over 70 years with displaced FNF	44.4	87.5	100.0	83.3	75.0
De Jong et al. (2019) Delirium after hip hemiarthroplasty for proximal femoral fractures in elderly patients: risk factors and clinical outcomes	44.4	75.0	100.0	66.7	67.8
Gottshalk et al. (2015) The Impact of Incident POD on Survival of Elderly Patients After Surgery for Hip Fracture Repair	55.6	75.0	100.0	66.7	71.4
Krogseth et al. (2013) Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients	55.6	75.0	100.0	100.0	75.0
Malik et al. (2018) Incidence, risk factors and clinical impact of POD following ORIF for hip fractures: an analysis of 7859 patients from the ACS-NSQIP hip fracture procedure targeted database	75.0	62.5	100.0	66.7	74.1
Mosk et al. (2017) Dementia and delirium, the outcomes in elderly hip fracture patients	75.0	62.5	100.0	100.0	81.4
Radinovic et al. (2015) Estimating the effect of incident delirium on short-term outcomes in aged hip fracture patients through propensity score analysis	44.4	87.5	80.0	83.3	75.0
Tahir et al (2018) Risk factors for onset of delirium after NOF fracture surgery: a prospective observational study	66.7	75.0	100.0	66.7	75.0

(87.8%), while delayed POD survival (83.6%) did not differ significantly from control (87.8%), p=0.579. [15] Mosk et al. mentioned POD patients had a higher incidence of mortality < 6 months (30.1%, P<0.001) [20]. Malik et al. showed that POD gave OR 2.04 for 30-day mortality (p < 0.001) [19]. Belleli et al. revealed that POD was independently associated with 6-month mortality and that each POD day increased hazard of dying by 17% [14].

Several articles were unable to find the results significant for increased mortality. Gottshalk et al. initially reported decreased survival, yet on Cox regression this became insignificant; HR 1.25 (CI [0.92-1.48]) [17]. Krogseth et al. combined institutionalization with mortality for composite risk analysis, which failed to reach statistical significance (AOR: 2.07, CI 0.88-4.89) [18]. Tahir et al. claimed 1-year mortality was significantly higher with POD (25.7%) compared to patients without delirium (15%) p = 0.026. Mortality within 30-days followed the same trend (10% vs. 6%) however did not reach statistical significance [22]. In Randovic et al. neither models of confounding showed 1-month mortality as a statistically significant hazard[21].

Medical Complications

Four studies dealt with medical complications. Arshi et al reported POD independent associations with higher coincidence of postoperative pneumonia, UTI, CVA, MI, hospital readmission and sepsis within 30 days[13]. Mosk et al. also displayed a higher rate of complications (48.5%, P<0.001) [20] while Malik et al. reported increased 30-day readmissions with POD (OR 1.80; p < 0.001) [19]. In Randovic et al., POD was a higher age adjusted risk of re-intervention plus death (OR 2.56), complications (OR 2.66) and higher severity complications (B = 0.83, P = 0.027). With more variate adjustments, a higher risk of re-intervention plus death (OR 7.16) and a longer LOS (B = 5.08) remained [21].

Institutionalization

Five studies investigated discharge location following POD. Arshi et al. mentioned POD was associated with greater discharge to (OR 1.65), and prolonged stay in, inpatient facilities (OR 1.79) [13]. In De Jong et al., POD patients without dementia, vs. control (no POD), were significantly more often discharged to nursing homes (OR 7.06) or semi-independent nursing homes (OR 11.4) [16]. Mosk et al reported that POD was significantly associated with nursing home admission (91.8%, P<0.001) [20]. Malik et al. stated POD lead to significantly higher odds of non-home discharge (OR 1.79) [19]. Krogseth et al. through logistic regression analysis concluded delirium remained a significant predictor of institutionalization (AOR: 5.50) [18].

Length of Hospital Stay (LOS)

6 studies examined the effect on LOS. Arshi et al. reported increased LOS [13]. However De Jong et al. stated greater LOS for the non-dementia POD group was not significant (P=0.128) [16]. Mosk et al described an increased LOS (median 6 days [IQR: 6], P=0.002) for POD patients [20]. For Malik et al. LOS was also significantly associated with POD. Compared with 0-3 day stay POD was associated with LOS 4-6 days (OR 1.63; p<0.001 and >6 days (OR 3.30; p< 0.001). [19] Tahir et al stated that the presence of delirium was associated with significantly increased LOS (average 13 days vs. 10 days, p = 0.001). [22] Randovic et al. also reported a prolonged LOS in POD (B = 5.75, P < 0.001) [21].

Discussion

Mortality

The results on mortality were far from conclusive, damaged by inconsistencies in follow-up periods, sampling size, and analysis. The articles showed weak statistical evidence for POD as a predictor of increased mortality [16], or it failed to achieve significance based on Kaplan-Meier survival analysis [17]. In Randovic et al., both extensive risk adjusted models failed to show that POD was a statistically significant hazard for 1-month mortality [21]. Yet a study with fewer confounding variables, Malik et al., found an association with 30-day mortality [19]. The exclusion of preoperative delirium perhaps explains Gottshalk et al. finding that, on Cox regression, POD was not significant for mortality [17]. This patient group has been shown in other studies to be at significant risk of POD [16, 20, 22]. Some studies perhaps lacked a substantial sample size to reach statistical significance. For example, in Tahir et al. 70 patients had POD, and 30-day mortality trends, while consistent, were insignificant [22]. Similarly cer-

tain papers deemed a p-value of <0.05 was enough for statistical significance which may redefine some results [15, 16]. Furthermore, the quality of statistical analysis differed, some lacking confounding [13, 19].

There is a certain inclination towards an association between POD and early mortality, yet this review is relatively consistent in showing that following adjustment for confounders significant associations of POD with mortality were unlikely [14].

Other Outcomes

There is more coherence, but perhaps less scrutiny, when dealing with other measured outcomes. POD was shown to have associations with complications [20], and hospital readmissions [13,19]. Arshi et al. also showed a greater rate of specific complications with POD [13]. The two models in Randovic et al. provided further backing to this, showing higher risk when adjusted for age for both of the aforementioned variables. The presence of POD was also associated with a higher severity complication score. With adjustment, POD remained a high risk for re-intervention plus death and a longer LOS [21].

LOS was conclusively associated with POD [13, 18, 19, 20, 22] Yet one study which stratified for dementia patients – a strongly associated risk for POD, had a non-significance to this association [16]. Most of these studies recognised the limitation of this for LOS as an outcome, due to the inability to establish the direction of the relationship between both variables.

Similarly, with institutionalisation, there was a relatively consistent association with POD across studies that measured it. [13, 16, 18, 19, 20,]. While many lacked conclusive confounding, Krogseth et al. through logistics regression analysis showed POD as the initiation of a detrimental functional process [18]. POD was also shown to have the greatest impact on patients who were already impaired. Thus, with all outcomes it is difficult to definitively establish POD as the cause.

Limitations

Throughout the studies there were certain issues with external validity, and other aspects of quality. Often sample sizes were small, only three papers having over 500 participants [13, 19, 20], with POD patients a smaller subset within these samples. Four papers were deemed unrepresentative in critical appraisal [15, 16, 17, 18]. Some acknowledged a reason for exclusion, but there is a benefit instead to stratifying these patients when included to get a proper picture.

Most of the studies acknowledged the difficulty in concluding that any of the outcomes were a direct cause from POD, given an admission that healthier patients are less vulnerable to the development of delirium and more resistant to its adverse outcomes if they become delirious [18]. Again assessment of confounding variables is a crucial issue here.

The field of knowledge itself must also be critiqued. There was a frustrating contrast in results based on lack of consistency and comparability of study design. A primary example of this was the diagnosis of POD. Most used the established DSM-IV tools and CAM algorithm but within this, there was variety. These assessments were carried out differently, e.g. every day [21] or once off [17]. Some also used additional techniques such as clinical notes reviewing and DOSS scores [20]. There were more disparities including stratifying dementia patients, delirium subtyping, missing hypoactive delirium, exclusion of certain surgical techniques, which all adds to the complexity involved in answering the review question. There is the possibility of bias within the papers, particularly single-centre studies performed by service providers e.g. Choi et al [15].
Other limits of this review would be time constraints while on full time placement, personal research and review inexperience, lack of access to full texts. As the sole reviewer, author bias is a major limitation on my part.

Conclusion

This review cannot draw any distinct conclusions from papers reviewed, and is forced instead to examine the state of the research field, which is seemingly clouded by low-quality outcome measurement – particularly of mortality - statistical variance, and general lack of consistency across the field. Thus, future research needs to focus on effective external validity of mortality claims. [24] Similarly there is a gap in the literature for measurement of personal impacts on patients, such as PTSD and depression. The issue of increased age and comorbidities associated with POD clouds the interpretations of these statistics and only multivariate regression models can address these issues.

Nevertheless, the need for prevention of POD was echoed throughout, given relative coherence on the less fatal negative effects, queries over increased mortality rate, and a background of increasing hip fracture prevalence. This should force action in the current lack of structured follow-up for these patients, [15] due to the great burden of POD on healthcare costs, patients, and families.

References

1. British Orthopaedic Association-British Geriatrics Society. The Care of Patients with Fragility fractures ("the Blue Book"). London: 2007
2. Muir SW, Yohannes AM. The Impact of Cognitive Impairment on Rehabilitation Outcomes in Elderly Patients Admitted with a Femoral Neck Fracture: A Systematic Review. Journal of Geriatric Physical Therapy. 2009;32(1):24-32.
3. Gullberg B, Johnell O, Kanis J. World-wide Projections for Hip Fracture. Osteoporosis International. 1997;7 (5):407-413.
4. Ariza-Vega P, Lozano-Lozano M, Olmedo-Requena R, Martín-Martín L, Jiménez-Moleón J. Influence of Cognitive Impairment on Mobility Recovery of Patients With Hip Fracture. American Journal of Physical Medicine & Rehabilitation. 2017;96(2):109-115.
5. National Report, Irish Hip Fracture Database. 2018
6. Ondeck NT, Bohl DD, Bovonratwet P, et al. Predicting Adverse Outcomes After Total Hip Arthroplasty: A Comparison of Demographics, the American Society of Anesthesiologists class, the Modified Charlson Comorbidity Index, and the Modified Frailty Index. J Am Acad Orthop Surg. 2018;26(20):735–743.
7. Klestil T, Röder C, Stotter C, et al. Impact of timing of surgery in elderly hip fracture patients: a systematic review and meta-analysis. Sci Rep. 2018;8(1):13933.
8. Chang W, Lv H, Feng C, et al. Preventable risk factors of mortality after hip fracture surgery: Systematic review and meta-analysis. Int J Surg. 2018;52:320–328.
9. Viramontes O, Luan Erfe B, Erfe J, Brovman E, Boehme J, Bader A et al. Cognitive impairment and postoperative outcomes in patients undergoing primary total hip arthroplasty: A systematic review. Journal of Clinical Anesthesia. 2019;56:65-76.
10. Oh S, Park J. Postoperative delirium. Korean Journal of Anesthesiology. 2019;72(1):4-12.
11. Lundström M, Stenvall M, Olofsson B. Symptom Profile of Postoperative Delirium in Patients With and Without Dementia. Journal of Geriatric Psychiatry and Neurology. 2012;25(3):162-169.
12. Aldecoa C, Bettelli G, Bilotta F, Sanders R, Audisio R, Borozdina A et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. European Journal of Anaesthesiology. 2017;34(4):192-214.
13. Arshi A, Lai W, Chen J, Bukata S, Stavrakis A, Zeegen E. Predictors and Sequelae of Postoperative Delirium in Geriatric Hip Fracture Patients. Geriatric Orthopaedic Surgery &Rehabilitation. 2018;9
14. Bellelli G, Mazzola P, Morandi A, Bruni A, Carnevali L, Corsi M et al. Duration of Postoperative Delirium Is an Independent Predictor of 6-Month Mortality in Older Adults After Hip Fracture. Journal of the American Geriatrics Society. 2014;62(7):1335-1340.
15. Choi Y, Kim D, Kim T, Lim T, Kim S, Yoo J. Early postoperative delirium after hemiarthroplasty in elderly patients aged over 70 years with displaced femoral neck fracture. Clinical Interventions in Aging. 2017 (12):1835-1842.
16. de Jong L, van Rijckevorsel V, Raats J, Klem T, Kuijper T, Roukema G. Delirium after hip hemiarthroplasty for proximal femoral fractures in elderly patients: risk factors and clinical outcomes. Clinical Interventions in Aging. 2019;(14):427-435.
17. Gottschalk A, Hubbs J, Vikani A, Gottschalk L, Sieber F. The Impact of Incident Postoperative Delirium on Survival of Elderly Patients After Surgery for Hip Fracture Repair. Anesthesia & Analgesia. 2015;121 (5):1336-1343.
18. De Marchis GM, Foderaro G, Jemora J, Zanchi F, Altobianchi A, Biglia E, Conti FM, Monotti R, Mombelli G. Mild cognitive impairment in medical inpatients: the Mini-Mental State Examination is a promising screening tool. Dement Geriatr Cogn Disord. 2010; (29):259 –64.
19. Krogseth M, Wyller T, Engedal K, Juliebø V. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. Journal of Psychosomatic Research. 2014;76(1):68-74.
20. Malik A, Quatman C, Phieffer L, Ly T, Khan S. Incidence, risk factors and clinical impact of postoperative delirium following open reduction and internal fixation (ORIF) for hip fractures: an analysis of 7859 patients from the ACS-NSQIP hip fracture procedure targeted database. European Journal of Orthopaedic Surgery & Traumatology. 2018;29(2):435-446.
21. Mosk C, Mus M, Vroemen J, van der Ploeg T, Vos D, Elmans L et al. Dementia and delirium, the outcomes in elderly hip fracture patients. Clinical Interventions in Aging. 2017;(12):421-430.
22. Radinovic K, Markovic-Denic L, Dubljanin-Raspopovic E, Marinkovic J, Milan Z, Bumbasirevic V. Estimating the effect of incident delirium on short-term outcomes in aged hip fracture patients through propensity score analysis. Geriatrics & Gerontology International. 2014;15(7):848-855.
23. Tahir M, Malik S, Ahmed U, Kozdryk J, Naqvi S, Malik A. Risk factors for onset of delirium after neck of femur fracture surgery: a prospective observational study. SICOT Journal. 2018;4(27).
24. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. Anesthesiology. 2017;127(1):78-88.
25. Sanders R, Pandharipande P, Davidson A, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. BMJ. 2011;343(20:1): 4331-4334.

[This page has been intentionally left blank. Please turn over.]

Evaluation of the Relationship Between Thyroid Cancer and the Concurrent Detection of Thyroid Nodules *on the Background of Primary Hyperparathyroidism*

By Alisha Poppen[1]

Reviewed by Dr. Collette Hand[2] and Dr. John Mackrill[2]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of Pathology, School of Medicine, University College Cork, Cork,

Abstract

Introduction

Primary Hyperparathyroidism (PHPT) is commonly caused by a benign parathyroid adenoma that results in overactivity of the gland and subsequent hypercalcemia due to elevated parathyroid hormone (PTH). This endocrine pathology is associated with thyroid cancer, specifically Papillary Thyroid Cancer (PTC). However the explanation for their synchronous presentation is unknown. Moreover, it causes diagnostic and treatment challenges that impact patient outcomes.

Aims and Objectives

To critically analyze published research to address the relationship between PHPT and thyroid cancer, the role of ultrasound imaging in detecting sinister thyroid nodules in PHPT patients and the features of PHPT that predispose the risk of thyroid malignancy.

Study Design

Literature Review

Methodology

Electronic database searches of PubMed and CINAHL Plus through EBSCOhost were conducted using the keywords “primary hyperparathyroidism”, “thyroid nodules” and “thyroid cancer”. Following application of filters and removal of duplicates, 627 relevant results remained. Articles were screened for eligibility based on predetermined selection criteria. Following a review of titles and abstracts, 10 peer-reviewed articles were chosen for further analysis. The studies included were critically appraised using the EBL Critical Appraisal Checklist.

Results

10 articles were examined, 2 were prospective cohort studies and 8 were retrospective cohort studies. All studies involved exhaustive medical chart reviews of patients with PHPT, to investigate the concomitance of thyroid malignancy. Six studies established cervical ultrasound as the optimal method of recognition and preoperative localization of thyroid and parathyroid lesions. Overall, the incidence of thyroid cancer among PHPT patients ranged between 2.9% to 32.9%. Four studies established age, gender and PTH levels as risk factors.

Conclusion

The existing literature is consistent with previous studies and purports that individuals with a background of PHPT are at an increased risk of thyroid cancer. Furthermore, the highest likelihood of identifying thyroid cancer is through preoperative localization of parathyroid adenomas by cervical ultrasound, in female patients over the age of 50.

Key Findings

Further research is needed to understand the underlying pathogenesis and genetic mechanisms that encompass the relationship between PHPT and thyroid cancer.

Introduction

The discrete anatomical location of the parathyroid glands remains a challenge in the treatment of its pathologies. Consisting of four small glands located on the posterior aspect of the thyroid gland, they function to maintain calcium homeostasis through the release of Parathyroid Hormone (PTH). The disease aetiology of Primary Hyperparathyroidism (PHPT) is commonly the result of a benign parathyroid adenoma that causes overactivity of the gland and subsequent hypercalcemia due to elevated PTH [1]. It is the third most common endocrine disorder, affecting 0.1-0.4% of the global population [2].

While thyroid disease is associated with PHPT, it is currently unknown whether the concurrent presentation of PHPT and Papillary Thyroid Cancer (PTC) is coincidental or causal, due to their intimate anatomical relationship [3]. Recent studies have determined that the incidence of PTC has risen dramatically in the past few decades, with the frequency of thyroid procedures and incidental findings of thyroid cancer increasing at an average rate of 10% [4-6]. It is known that the incidence of thyroid disorders in PHPT patients is significantly greater than the incidence of PHPT in patients with thyroid disorders, suggesting that the existing association is not bidirectional [7]. Additionally, the issue remains of whether PHPT is a risk factor for thyroid cancer or if cervical ultrasounds are resulting in overdiagnosis.

Routine screening of the parathyroid glands simultaneously incorporates evaluation of the thyroid gland. Preoperative diagnostic imaging for localizing parathyroid adenomas can also detect thyroid nodules [8]. These thyroid lesions are referred to as incidentalomas, which are asymptomatic yet warrant Fine Needle Aspiration Biopsy (FNAB) to rule out malignancy. Further neck exploration through invasive measures are associated with risks that outweigh the benefits if performed unnecessarily.

The existing evidence is inconclusive as to whether increased recognition of thyroid incidentalomas will improve health outcomes or lead to excessive thyroid interventions. Therefore, concurrent thyroid pathology and PHPT can be problematic for the healthcare provider's clinical and surgical decision-making regarding their patients.

The purpose of this literature review is to critically appraise the existing evidence of the relationship between detection of thyroid nodules and incidence of thyroid cancer on the background of PHPT. More importantly, it will provide insight on the impact of over-detection with diagnostic imaging and predictable risk factors on the concomitant pathologies. This is of clinical relevance as the benefits of surgical intervention for thyroid incidentalomas remain controversial. As clinical guidelines for management and treatment remain non-existent [7], it is imperative to determine the factors contributing to the concurrence of thyroid cancer and PHPT, in order to mitigate them.

Aims and Objectives

The primary objective of this paper is to critically analyze and evaluate the existing peer reviewed literature that address the following topics:

1) The relationship between PHPT and thyroid cancer

2) The role of ultrasound imaging in detecting sinister thyroid nodules in PHPT patients

3) The features of PHPT that predispose the risk of developing thyroid cancer

Methodology

Database Search

To obtain the articles for review, an electronic database search using PubMed and CINAHL Plus through EBSCOhost was conducted on January 11th, 2020. The purpose of this was to identify articles that were relevant to the topic of how PHPT is associated with the development of thyroid cancer. Themes incorporated in the primary search were "primary hyperparathyroid-

ism" and "thyroid cancer".

The following keywords were used on CINAHL Plus through EBSCOhost Database:

1) Primary Hyperparathyroidism

2) Thyroid Nodules

3) Thyroid Cancer OR Papillary Thyroid Carcinoma

The following keywords were developed and searched for using PubMed Database:

1) ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])

2) ("thyroid neoplasms"[MeSH Terms] OR ("thyroid"[All Fields] AND "neoplasms"[All Fields]) OR "thyroid neoplasms"[All Fields] OR ("thyroid"[All Fields] AND "cancer"[All Fields]) OR "thyroid cancer"[All Fields]) OR ("Crit Arts"[Journal] OR "CA Cancer J Clin"[Journal] OR "ca"[All Fields])

3) ("thyroid nodule"[MeSH Terms] OR ("thyroid"[All Fields] AND "nodule"[All Fields]) OR "thyroid nodule"[All Fields] OR ("thyroid"[All Fields] AND "nodules"[All Fields]) OR "thyroid nodules"[All Fields])

Application of Filters

The filters applied to both databases after the initial search are presented below in table 1:

Table 1
List of filters applied on EBSCOhost and PubMed .

Filter	Comment
Publication dates	2009-2020
Text Availability	Full Text
Language	English
Age	18+
Species	Humans

Selection Criteria

Table 2
Details the inclusion and exclusion criteria applied for the selection of the studies included in this review.

Inclusion Criteria	Exclusion Criteria
Relevant articles published within the past 10 years and available online with full-text, in English	Articles in other languages that are older than 10 years, without full-text
Peer reviewed articles in academic journals	Articles that are not peer-reviewed, case reports or animal studies
Studies evaluating the imaging results of adults +18 years with PHPT and thyroid nodules	Studies involving patients with MEN or previous thyroidectomy
Studies evaluating the genetic component thyroid cancer in PHPT patients	Studies evaluating the risk of non-thyroid related cancers from PHPT
Studies assessing the histological features of thyroid nodules	Studies evaluating benign thyroid nodules exclusively
Studies evaluating the relationship between PHPT and thyroid cancer	Studies that do not involve patients with PHPT
Studies assessing the diagnostic and prognostic markers of thyroid cancer	Studies assessing the diagnosis and management of PHPT

Quality Assessment

To assess the quality of each study, the EBL Critical Appraisal Checklist was applied to establish validity. The checklist assesses the study population, study design, data collection and results of each study. A score was calculated for the validity of individual sections and the overall paper.

Data Extraction

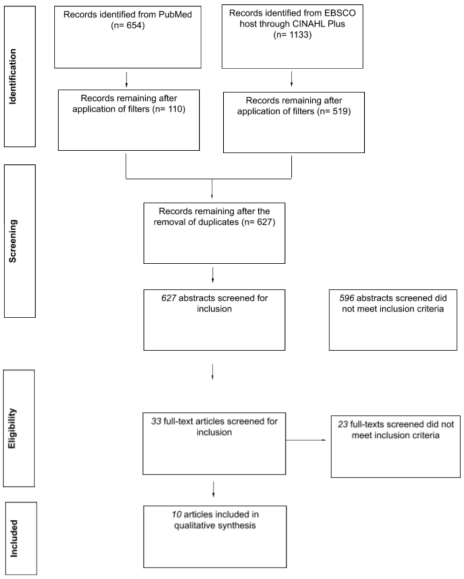
To evaluate each study, the following information was extracted:

I. First author, publication year
II. Title of study
III. Location of study
IV. Study objectives
V. Study design
VI. Sample size
VII. Methodology
VIII. Selection criteria
IX. Key findings
X. Strengths and limitations

Table 3
Reasons for Article Exclusion after Full-Text Review

Reason for Exclusion	Number
Case Report	15
Did not involve patients with PHPT	4
Evaluation of cancer not related to the thyroid	1
PHPT diagnosis and management	2
Assessment of benign thyroid nodules exclusively	1
TOTAL	**23**

Figure 1
Methodology of literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



Data Selection Process

On EBSCOhost, the initial search generated 1133 results, and was reduced to 519 after the application of filters from Table 1. On PubMed, the initial search produced 654 results, which was reduced to 110 upon application of the same filters. After collating all the results and removal of duplicates, 627 articles remained. Of the 627 abstracts screened, 596 articles did not fulfill the inclusion criteria. The remaining 33 full-text articles were then analyzed in more detail, with the application of the inclusion and exclusion criteria, and 10 articles were selected to be assessed in this literature review. Figure 1 depicts the study selection process.

Results

Association between PHPT and PTC

Nine studies assessed the relationship between PHPT and PTC to determine that there is an increased incidence of thyroid malignancy on the background of the parathyroid disorder [7,9,11-17]. The incidence of the concurrent pathologies ranged from 2.9% in the Yazici et al study [7], to 32.9% in the Scerrino et al study [14]. Thyroid nodules that were identified upon imaging of the parathyroid gland were the primary indicator of thyroid gland dysfunction.

Furthermore, Preda et al determined that the incidence of PTC is similar among PHPT and SHPT cohorts [13].

Table 4
Validity scores determined by the Evidence Based Librarianship (EBL) Checklist for the critical appraisal of peer-reviewed scientific articles

Study	Population Validity	Data Collection Validity	Study Design Validity	Results Validity	Overall Validity
Adler *et al.* 2010	40%	100%	100%	100%	86%
Barbaros *et al.* 2009	60%	100%	100%	67%	80%
Cetin *et al.* 2019	75%	100%	100%	100%	95%
Cuhaci *et al.* 2019	67%	100%	100%	67%	86%
Preda *et al.* 2019	80%	100%	100%	100%	95%
Scerrino *et al.* 2016	80%	80%	100%	50%	76%
Shen *et al.* 2019	60%	80%	100%	67%	76%
Vargas-Ortega *et al.* 2018	60%	100%	100%	83%	86%
Xue *et al.* 2016	60%	100%	100%	83%	85%
Yazici *et al.* 2015	40%	100%	100%	83%	81%

Risk factors of PTC in PHPT patients

Four studies established risk factors for developing PTC on the background of PHPT [11,13,16-17]. Age, gender and elevated PTH levels were determined to be risk factors ($p<0.05$), such that females over the age of 50 were dominant in the PHPT and PTC cohort (11,13,16). In contrast, Yazici et al did not find a meaningful correlation between PTC and age [7].

The role of ultrasound in PTC diagnosis

Six studies concluded that cervical ultrasound was the optimal method of recognition and preoperative localization of suspicious thyroid and parathyroid lesions [7,9-10,12,14-15]. Two studies determined that nuclear imaging with Tc99m sestamibi scintigraphy and ultrasound should be used as complementary diagnostic tools in detecting PTC [12,14]. Adler et al found that routine ultrasound in PHPT patients is beneficial in discovering occult thyroid pathology and determining appropriate interventions [9].

Upon completion of a comprehensive literature search of the EBSCOhost (CINAHL Plus) and PubMed databases, 10 articles were chosen to be analyzed. These articles were peer-reviewed, published in English within the past 10 years, had full-text available, involved human partici-

pants and investigated the relationship between PHPT and thyroid cancer. A total of 2 prospective cohort studies and 8 retrospective cohort studies were included. The validity scores of each paper are elucidated in Table 4 and the key findings from each paper is summarized in Table 5. Additionally, three main themes emerged from the qualitative synthesis of the chosen articles.

The quality of each study was objectively assessed with the EBL Critical Appraisal tool. The validity of each section, in addition to the overall validity was calculated based on a predetermined formula and deemed acceptable within each study.

Discussion

Following a thorough analysis of 10 peer-reviewed articles that were published within the past 10 years, it is evident that PHPT is associated with concomitant thyroid malignancy. The purpose of this literature review was to investigate the relationship between the two diseases, identify the risk factors and explore the influence of diagnostic imaging on the incidence of thyroid cancer with a background of PHPT.

Findings

Nine studies identified thyroid cancer among PHPT patients on the presence of thyroid nodules. In all cases, these nodules were incidental findings that were recognized while investigators were examining parathyroid adenomas. The wide range of incidence can be explained by differences in the size of the cohorts and geographical, environmental and cultural factors in each study. Furthermore, the existing spatial relationship regarding the anatomical location of parathyroid and thyroid lesions warrants further investigation as to whether a temporal relationship exists.

From the retrospective chart reviews, 4 studies identified that sex, age, hormone levels and size of thyroid nodules are risk factors for the development of PTC in PHPT patients. Specifically, Vargas-Ortega et al observed an increase in the incidence of thyroid cancer among females older than 50 years with elevated PTH levels [16]. A stepwise multivariate logistic regression analysis was conducted to validate this correlation between clinical and biochemical characteristics and thyroid cancer. Conversely, the Yazici et al study did not support these findings [7]. Therefore, there is the possibility of selection bias regarding the medical records that were chosen for review.

All studies involved the use of cervical U/S in various capacities. However, 6 studies investigated its role as the primary tool for screening and diagnostic purposes. Adler et al [9], found that the high-resolution ultrasound imaging has greater specificity than sensitivity for detecting parathyroid adenomas. This conclusion was further supported by the Barbaros et al [10], study, which discovered that false positive results increase with larger thyroid nodules that are posteriorly located. However, the limitation of using ultrasound imaging is that it cannot detect nodules less than 1 cm. Despite requiring a FNAB to confirm the presence of thyroid malignancy with histopathology, Shen et al [15] discovered that lesions identified on imaging positively correlate with sinister findings. This advantage of early detection is not without the disadvantage of over-diagnosis. It is established in literature that routine U/S for PHPT patients can mitigate unnecessary thyroid interventions (9). In contrast, the concurrent detection of papillary microcarcinoma, a small sized and non-invasive type of PTC, has led to an increase in thyroidectomies [7]. This is controversial because there were no accompanying clinical symptoms to warrant gland excision and the risks of the procedure outweigh no intervention. Although it may be efficient and accurate, the information obtained from ultrasound imaging should always be considered in the context of the complete clinical picture.

Quality and Validity

The EBL Critical Appraisal Checklist was used to determine that the studies included in this literature review are of good to high quality, as the overall validity scores ranged between 76% to

95%. Among individual categories, population validity varied considerably. This is due to the relatively small sample size in most of the retrospective cohort studies. Consequently, the validity of the results was affected, and the statistical power was reduced.

Strengths and Limitations

A major strength of this literature review is that it provides a wholistic summary of the topic of study. Firstly, the 10 selected articles were chosen from 2 different online sources, which reduced database bias and allowed for a broader scope of scientific publications to be incorporated. Secondly, the studies were conducted in various geographical medical centers and similar trends between PHPT and thyroid cancer were identified, thereby minimizing location bias. Thirdly, most of the studies highlighted the involvement of an individual or small team of medical technicians and pathologists to obtain diagnostic data from the patients. This minimized user bias and strengthened the validity of the results. Finally, the credibility of the findings in each study were further supported by the use of appropriate statistical tests. Specifically, all studies assessing categorical variables used Fischer's chi-square test with a p-value of less than 0.05 to establish statistical significance.

Equally important in this review are the limitations presented in the studies. Given the nature of the research question, the predominant implementation of the retrospective cohort study design posed certain restrictions. Although it is ethical and feasible, these observational studies can only determine correlations, rather than causal links between variables. Furthermore, extracting patient data from their medical records are prone to information bias and confirmation bias. Researchers cannot control for confounding variables and differences in the methods by which patients underwent clinical examinations or thyroid surgery. Notably, most studies were limited to a small sample size of PHPT patients. This is disadvantageous because it minimizes the reliability and external validity of the clinical outcomes. Thus, these factors must be considered when identifying trends in chart reviews, in order to obtain objective conclusions.

Future Research

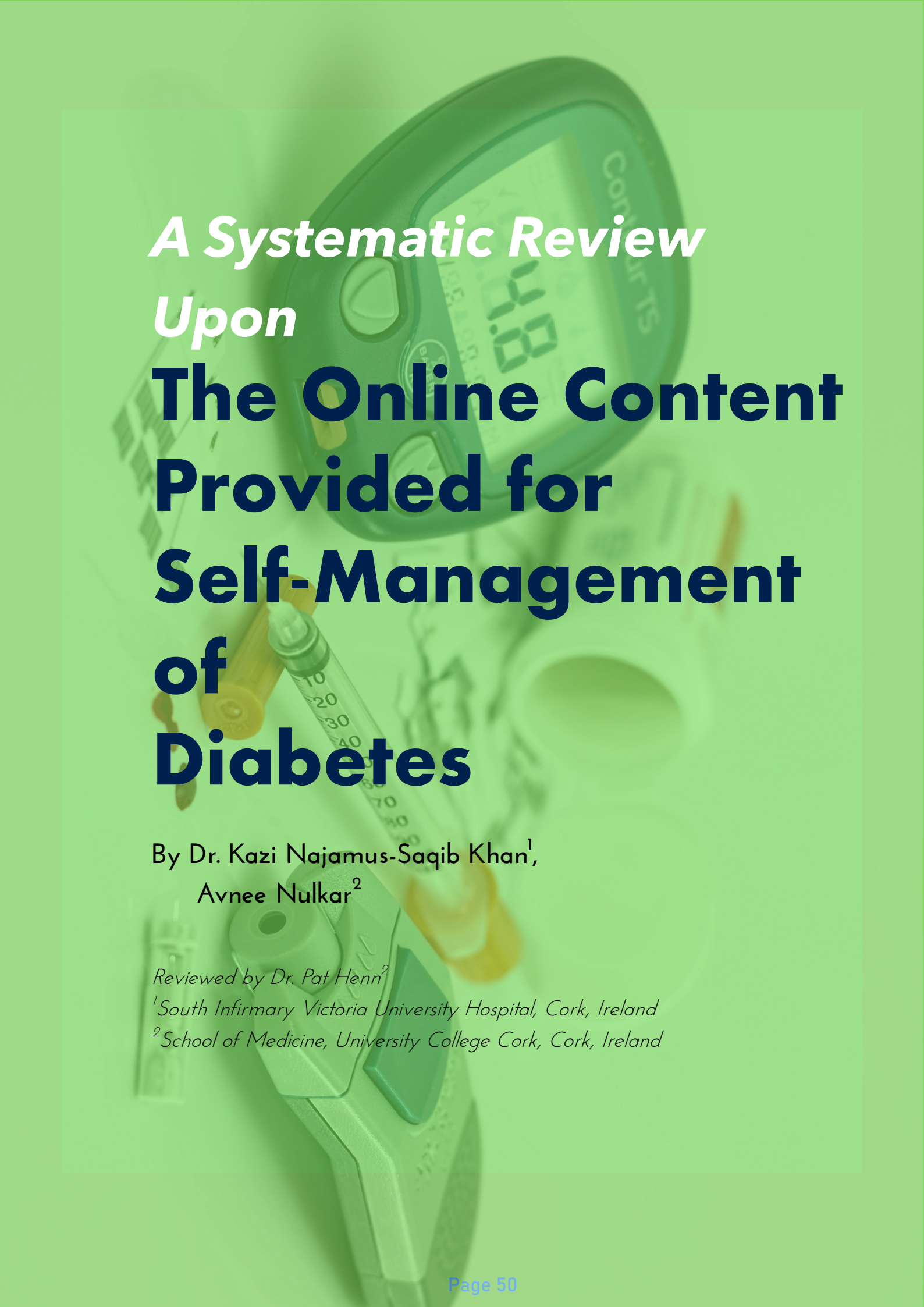
Although the existing research concludes that an association between both diseases exist, it fails to explore the mechanisms by which PHPT and thyroid cancer are related. This provides an avenue for future research regarding the pathogenesis or genetic factors that may be implicated. This would be beneficial in determining whether the concurrent pathologies are incidental or predictable. Thus, the existing hypothesis generating retrospective study designs need to be supported with evidence from prospective clinical studies.

Conclusion

The existing evidence suggests that individuals with a background of PHPT are at an increased risk of thyroid cancer. This literature review not only focuses on this relationship, but also analyzes the use of ultrasonography in diagnosis and potential risk factors. The clinical importance of these findings is that it will aid in predicting the occurrence of thyroid cancer in PHPT patients, thereby enabling future physicians to prevent its occurrence rather than cure it. Therefore, the impact of detecting incidental thyroid lesions prior to any clinical manifestations must be further investigated to determine the best course of action that beneficiates patient outcomes.

References

1. Center NP. Parathyroid Glands, High Calcium, and Hyperparathyroidism [updated Jan 15 2020. Available from: https://www.parathyroid.com/.
2. Heath D. Primary hyperparathyroidism Clinical presentation and factors influencing clinical management. Endocrinol Metab Clin North Am. 1989;18:631-46.
3. Wilson SD DK, Wang TS Primary hyperparathyroidism with a history of head and neck irradiation: The consequences of associated thyroid tumors. Surgery. 2011;150:869-77.
4. Wright M-C, Jensen K, Mohamed H, Drake C, Mohsin K, Monlezun D, et al. Concomitant thyroid disease and primary hyperparathyroidism in patients undergoing parathyroidectomy or thyroidectomy. Gland surgery. 2017;6 (4):368-74.
5. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, et al. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ journal of surgery. 2006;76(3):123-6.
6. Bradly DP, Reddy V, Prinz RA, Gattuso P. Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. Surgery. 2009;146(6):1099-104.
7. Yazici P, Mihmanli M, Bozdag E, Aygun N, Uludag M. Incidental Finding of Papillary Thyroid Carcinoma in the Patients with Primary Hyperparathyroidism. Eurasian J Med. 2015;47(3):194-8.
8. Wilhelm SM WT, Ruan DT et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016;151 (10):959-68.
9. Adler JT, Chen H, Schaefer S, Sippel RS, Adler JT, Chen H, et al. Does routine use of ultrasound result in additional thyroid procedures in patients with primary hyperparathyroidism? Journal of the American College of Surgeons. 2010;211(4):536-9.
10. Barbaros U, Erbil Y, Salmashoglu A, Issever H, Aral F, Tunaci M, et al. The characteristics of concomitant thyroid nodules cause false-positive ultrasonography results in primary hyperparathyroidism. American Journal of Otolaryngology. 2009;30(4):239-43.
11. Cetin K, Sikar HE, Temizkan S, Ofluoglu CB, Ozderya A, Aydin K, et al. Does Primary Hyperparathyroidism Have an Association with Thyroid Papillary Cancer? A Retrospective Cohort Study. World J Surg. 2019;43(5):1243-8.
12. Cuhaci N, Ozdemir D, Polat B, Arpaci D, Yildirim N, Yazgan AK, et al. Concomitant thyroid lesions in patients with primary hyperparathyroidism. Asian J Surg. 2017;40 (5):338-44.
13. Preda C, Branisteanu D, Armasu I, Danila R, Velicescu C, Ciobanu D, et al. Coexistent papillary thyroid carcinoma diagnosed in surgically treated patients for primary versus secondary hyperparathyroidism: same incidence, different characteristics. BMC Surg. 2019;19(1):94.
14. Scerrino G, Attard M, Lo Piccolo C, Attard A, Melfa GI, Raspanti C, et al. The coexistence of primary hyperparathyroidism and thyroid nodules: should the preoperative work-up of the parathyroid and the thyroid diseases be specifically adjusted? G Chir. 2016;37(3):123-9.
15. Shen J, Wu Q, Wang Y. The role of ultrasound in the diagnosis of the coexistence of primary hyperparathyroidism and non-medullary thyroid carcinoma. BMC Med Imaging. 2019;19 (1):7.
16. Vargas-Ortega G, Balcázar-Hernández L, González-Virla B, Ramírez-Rentería C, Nieto-Guzmán O, Garrido-Mendoza AP, et al. Symptomatic Primary Hyperparathyroidism as a Risk Factor for Differentiated Thyroid Cancer. Journal of Thyroid Research. 2018:1-6.
17. Xue Y, Ye ZQ, Zhou HW, Shi BM, Yi XH, Zhang KQ. Serum Calcium and Risk of Nonmedullary Thyroid Cancer in Patients with Primary Hyperparathyroidism. Med Sci Monit. 2016;22:4482-9.



A Systematic Review Upon

The Online Content Provided for Self-Management of Diabetes

By Dr. Kazi Najamus-Saqib Khan[1],
Avnee Nulkar[2]

Reviewed by Dr. Pat Henn[2]
[1]South Infirmary Victoria University Hospital, Cork, Ireland
[2]School of Medicine, University College Cork, Cork, Ireland

Abstract

Background

Diabetes is a major illness that requires appropriate education in order to increase one's understanding of self- management. With the advancement of the internet, the proliferation of online health-related content in supporting the management of chronic illnesses like diabetes has been ongoing; however, little is understood on the sort of acceptable and/or effective information attainable online.

Objective

The aim of this review is to evaluate the current literature in hindsight of online management in diabetes whilst establishing the effectiveness of online management tools, the quality of the online information, and the methods of obtaining online information.

Methods

A series of systematic searches of onlinedatabases were conducted in accordance with strictly defined inclusion and exclusion criteria relevant to the research question. Additionally, an evidence-based literature (EBL) checklist tool was used to assess the methodological and reporting quality of each study. Each article was peer-reviewed and screened for any biases.

Results

A result of 11 electronic searches were critically appraised using the EBL appraisal checklist tool and all were found to have overall validity. The results indicate an increase use of online technology to empower an understanding of one's own health. Web-based tools like social media were useful in promoting the management of diabetes but were not able to provide quality information.

Conclusion

Current research indicates the need for more investigation and future development of readily accessible and qualitative information in order to support the self-management of diabetes.

Introduction

Diabetes is one of the most renowned illnesses. This chronic illness is characterized with hyperglycemia precipitating a variety of clinical issues. Both T1DM and T2DM contribute to major cardiovascular implications that is the world leading cause of death.

The WHO estimated 422 million people with diabetes in 2015 [2]. In particular, Ireland estimated to have 225,840 people living with diabetes. International Diabetes Federation Diabetes Atlas further estimated that there are 207,490 people with diabetes in Ireland in the 20- 79 age group and could exceed up to 278,850 peopleby 2030 [1]. Management for this critically chronic condition is essential in healthcare and improvement in health awareness about diabetes and disease management should be tailored through continuous efforts via patient education [3].

Given that patients provide the majority of their own diabetes care, patients' self- management training has progressively become recognized as an important strategy to improve quality of care [4]. It has been shown that structured patient education programs reduce the risk of diabetes related complications four-fold [5]. Yet, participation in these self-management programs are low [4]. Interventions like structured patient education programs rely heavily upon patient motivation. The efficacy of these interventions depends on personal motivation of patients, which further speaks to the impact of self-management [4]. This gap has the potential to be bridged through the use of online resources on diabetes.

Online forums and programs have shown to be effective for a number of chronic conditions [6]. Even though there is a proportionate relationship between the use of online content and chronic conditions, information on the effectiveness of the online information specifically in the field of

management in diabetes is less understood. This literature review aims to tackle this by assessing the current literature on the efficacy of online content provided for the management of diabetes. It is hoped that this literature will help identify the gaps in the current online resources and may highlight the need for assistance in the area in the future.

Objectives

The objectives of this review are to analyze the published literature on the type of online content available for the management of diabetes to establish:

1) The effectiveness of the online management tools
2) The quality of online information on diabetes
3) The method in obtaining online information

Methods

An electronic search was carried out on two databases to identify the studies available in answering the research objectives of this review.

Search Strategy

The databases used were PubMed and Cochrane Library.

The search terms used for these databases were:

"Diabetes Online Knowledge Quality"

1) (("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields]
   AND
2) "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields])
   AND
3) online[All Fields]
   AND
4) ("knowledge"[MeSH Terms] OR "knowledge"[All Fields]))
   AND
5) ("quality"[MeSH Terms] OR "quality"[All Fields])

PubMed Database:

1) *The initial search prior to any filters brought 272 search results.*
2) *The following filters were added to reduce this field of results to a more specific set: publications within the past 5 years resulted in 168 results.*
3) *Additional limitations of free full text availability yielded 80 search results.*
4) *A filter of species of humans yielded 48 results respectively.*
5) *The remaining articles were reviewed manually by reading the titles and abstracts and a further 38 were found to be irrelevant and subsequently removed. This led to a final 10 relevant articles.*

An additional search was undertaken using Cochrane Library. The search was as follows: ***"quality online information on diabetes"***

1) *Initially, this produced 96 results and were thoroughly reviewed on the basis of the abstract and methodological approach.*
2) *This concluded with a final outcome of 3 studies.*
3) *Two of the data sets were unavailable for free full text access because of the requirement of an accessible login account, which produced one review.*

Filters:

- *Article Type – Research Articles*
- *Years Published – Published between 2013 -2018*
- *Text Availability – Open Access*

Inclusion Criteria:

- *English Language*
- *Adults age greater than or equal to 18*
- *Patients knowledge or education on diabetes assessed in study*

Exclusion Criteria:

- *Studies unavailable in English*
- *Studies that did not involve human participants*
- *Irrelevant or dissimilar methodological approach*

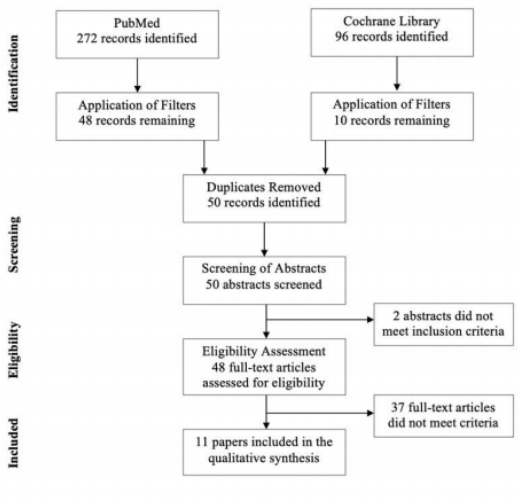
Results

Analysis of the validity of the study design found 10 of 11 studies obtained overall validity (validity score > 75%) [5-12, 14-15]. Only 4 of the 11 studies obtain validity in all subsections [5, 7, 10,16] with the remaining 7 studies having at least 1 subsection that did not achieve validity. This lack of validity was primarily due to restrictions posed by sample population and results achieved, which consistently introduced a lack of sample size or inappropriate subset analysis as a major, rather than minor, focus within the articles. The study instruments, which consisted of questionnaires, are often not validated and not included in the publication. Additionally, consent and ethical approval was often not mentioned in the publication.

Abbreviations Used in Table:

- ***DM:*** *Diabetes Mellitus*
- ***N:*** *Sample Size*
- ***T2DM:*** *Type 2 Diabetes Mellitus*
- ***RCT:*** *Randomised Control Trial*
- ***GDM:*** *Gestational Diabetes Mellitus*
- ***CMHDs:*** *Common Mental Health Disorders*
- ***PA:*** *Patient Activation*
- ***INT:*** *Intervention*
- ***UC:*** *Usual Care*
- ***DOC:*** *Diabetes Online Community*

Figure 1: Study Selection Criteria



Discussion

This review aimed to assess the efficacy of online sources and the manner in which searches were conducted. There were seven studies that attempted to evaluate the effectiveness of online information in diabetes self-management [6, 8, 9, 10, 11,15,16]. The other four studies assessed the behavior online information was obtained [7, 12, 13, 14]. From the studies, seven used a qualitative study design [7, 8, 11, 12, 13, 14, 15,], three with a randomized control trial [6, 10, 16], and one that used a web-based intervention [8].

Effectiveness of Online Tools in Management of Diabetes

From the results obtained above, the overall consensus indicated that web- based online tools proved to be a suitable way in promoting self-management of diabetes; however, online content provided very seldom accurate or readily accessible knowledge on the type of information provided. Studies by Sayakhot et al [8], Sadler et al [9], and Reininger et al [10] examined the knowledge gained from the use of online management tools. These studies indicated that the management of diabetes through an online platform is a good way in aiding self-management of diabetes. For example, Sayakhot designed an intervention using a web-based educational program for women with Gestational Diabetes Mellitus (GDM). The study found that the online program increased women's knowledge about managing their GDM. Though there was not a huge statistical gap of improvement between the intervention and comparison group predominantly due to both groups receiving an educational class beforehand, the online component provided a convenient way in self-learning of GDM for the intervention group and that access to the web-based education program at home proved as a useful source of reference for women with GDM [8]. Sadler et al. further validates this point after the study conducted that "patient referral to online tools is considered to be one key component of initial and ongoing diabetes self-management education and support and is recommended as a way to enhance and extend the reach of in-person diabetes education" [9]. Though the study from Reininger et al also agrees with this consensus, this particular research was based on a multi-ethnic approach and further found that diabetes-related information was less commonly sought online even amongst those at risk [10].

On the contrary, studies reported by Kingshuk [5] and Tang [15] did not have the same consensus. Their results founded only minimal evidence of improvement in diabetes management from the online systems. The RCT systematic review conducted by Kingshuk found that computer-based diabetes self-management interventions had limited evidence supporting their use and was poorly understood. This review also supported the suggestion that mobile phone-delivered interventions may be more effective than interventions delivered over the Internet. Within Tang's study, there was a statistical significance through online management of blood glucose between the interventional and usual care group. However, this statistically significant change had a rapid reduction in population mean Hemoglobin A1C at 6 and 12 months after randomization and was no longer statistically significant at 12 months. This study validates the assertion that diabetes self-management interventions often show evidence of short term benefits that may fade over time [5]. An assertion that should be looked closely into from the quality aspect in management of diabetes.

Quality of Online Information Provided in the Management of Diabetes

Though web-based tools may provide a useful way for the self-management of diabetes, the accessibility and quality of online information has been questioned. Research conducted by Crangle et al and Yu et al provide some indication to this. Crangle et al reported that the 10 open ended questions selected as a representative of patients' concerns about diabetes submitted to top-ranked websites across three countries failed to provide answers in their 2014 assessment. This was conducted again in a 2016 assessment and found only one answer of value for only 1 out of the 10 questions. The results showed that trusted and vetted online websites delivered general or out-of-context information online [7]. Over the course of two time periods in assessing online content, these results demonstrated the lack of quality online information available in answering specific patients questions about their diabetes. Yu et al. further signified this point from the web-based self - management site. Their results showed that participants not only wanted access to accurate knowledge about their condition but also easy-to-find answers about their diabetes care [14]. Both of these studies demonstrate the need of a readily accessible and quality online website in order to answer and promote self-management of diabetes.

Methods in Obtaining Online Information about Diabetes

Additional to evaluating the effectiveness and quality of online management of diabetes, this review aimed to seek the manner that online diabetes information was obtained. Only four studies detailed in this review provided descriptive in-depth analysis. The results from Fergie et al. provided an interesting correlation between young adults varying 18-30 years [13]. This study showed that the young adult population sought online health information varying from search engines to social media sites. This report provides the basis that social media was the primary tool in achieving the immediate distinctive goals for young adults. This research noted that since the widespread adoption of social media, user-generated health-related content has proliferated, particularly around long-term health issues such as diabetes [13]. A report from Magnezi further concluded that participation in an online health-related social network enhanced patients' self efficacy and empowerment, as they are given knowledge and tools to manage their chronic health condition more effectively [11]. On the other hand, Litchman results indicated that adults aged 53-71 in America accessed online information in another type of manner [12]. The diabetes online community was the main tool used by this elderly age group in attaining information. The diabetes online community was a way to discuss owns self-information online in order to increase knowledge with others for diabetes self-management. It was reported by Balkhi [6] that these types of forums had a high level of trust, social support, and knowledge gained. It was interesting to notice that younger adults were more inclined in using up-to-date software for self management compared to the older age group. Though there has been a proliferation of health related social media content, the quality of the information can be arguably lower compared with the diabetes online community.

Limitations & Future Research

There are variable limitations from the outcome of this paper. Pertaining to the articles, biases were screened for via peer-reviewed assessment of each study that met the inclusion criteria. Some of the studies suffered from a poor study population validity which was associated with response and non-response bias. Majority of the studies use web-based questionnaires or interventions as the primary means of data collection. It is unclear if the findings from the studies are truly representative of the population. The process of data collection may have also introduced bias since none of the measurement tools have been validated and the surveys used are often not published with the study. Lastly, because only one researcher was responsible for the evaluation of the papers, error in interpretation hence measurement bias cannot be fully eliminated.

Future research on the quality and quantity of online content for diabetes is required to provide effective information in order to aid self-management. Computer-based self-management interventions have the potential to provide a cost-effective option in reducing the burdens placed on patients and healthcare systems by this long-term condition.

Conclusion

Recent research regarding the self-management of diabetes through online platforms indicates that the topic is becoming increasingly characterized; however, when critically appraised, the quality of evidence was of insufficient means to draw a qualitative basis. In terms of the method of obtaining online information, the younger age population was less likely to access online support groups, compared to the elderly. The younger population were therefore the least effective in means of self-managing diabetes, compared to the elderly being more effective with their online community support groups. This review further dictated that web- based online tools proved to be a suitable way in promoting self-management of diabetes; however, online content provided very seldom accurate or readily accessible knowledge. More research should be conducted in order to provide an effective way in delivering readily accessible and quality- type of online information in the promotion of self-management of diabetes.

References

1. Mayo Clinic. (2018). Type 1 diabetes - Symptoms and causes. [online] Available at: https://www.mayoclinic.org/diseases-conditions/type-1- diabetes/symptoms-causes/syc-20353011 [Accessed 25 Jan 2018].

2. Sattar, H. (2017). Fundamentals of pathology. Chicago,Illinois: Pathoma.com, p.167.

3. Who.int. (2018). WHO | Diabetes mellitus. [online] Available at: http://www.who.int/mediacentre/factsheets/fs138/en/ [Accessed 25 Jan. 2018].

4. Almutairi KM. Quality of Diabetes Management in Saudi Arabia: A Review of Existing Barriers. Arch Iran Med. 2015;18(12):816-21

5. Yu CH, Parsons J, Mamdani M, Lebovic G, Shah BR, Bhattacharyya O, et al. Designing and evaluating a web-based self-management site for patients with type 2 diabetes--systematic website development and study protocol. BMC Med Inform Decis Mak. 2012;12:57.

6. Pal K, Eastwood SV, Michie S, Farmer A, Barnard ML, Peacock R, et al. Computer-based interventions to improve self-management in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2014;37(6):1759-66.

7. Balkhi AM, Reid AM, McNamara JP, Geffken GR. The diabetes online community: the importance of forum use in parents of children with type 1 diabetes. Pediatr Diabetes. 2014;15(6):408-15.

8. Crangle CE, Bradley C, Carlin PF, Esterhay RJ, Harper R, Kearney PM, et al. Soliciting and Responding to Patients' Questions about Diabetes Through Online Sources. Diabetes Technol Ther. 2017;19(3):194-9.

9. Sayakhot P, Carolan-Olah M, Steele C. Use of a web-based educational intervention to improve knowledge of healthy diet and lifestyle in women with Gestational Diabetes Mellitus compared to standard clinic-based education. BMC Pregnancy Childbirth. 2016;16(1):208.

10. Sadler MD, Saperstein SL, Carpenter C, Devchand R, Tuncer D, O'Brian C,et al. Community Evaluation of the National Diabetes Education Program's Diabetes HealthSense Website. Diabetes Educ. 2017;43(5):476- 85.

11. Reininger B, Mecca LP, Stine KM, Schultz K, Ling L, Halpern D. A type 2 diabetes prevention website for african americans, Caucasians, and mexican americans: formative evaluation. JMIR Res Protoc. 2013;2(2):e24.

12. Magnezi R, Bergman YS, Grosberg D. Online activity and participation in treatment affects the perceived efficacy of social health networks among patients with chronic illness. J Med Internet Res. 2014;16(1):e12.

13. Litchman ML, Rothwell E, Edelman LS. The diabetes online community: Older adults supporting self-care through peer health. Patient Educ Couns. 2017.

14. Fergie G, Hilton S, Hunt K. Young adults' experiences of seeking online information about diabetes and mental health in the age of socialmedia. Health Expect. 2016;19(6):1324-35.

15. Yu CH, Parsons JA, Hall S, Newton D, Jovicic A, Lottridge D, et al. User centered design of a web-based self-management site for individuals with type 2 diabetes - providing a sense of control and community. BMC Med Inform Decis Mak. 2014;14:60.

16. Tang PC, Overhage JM, Chan AS, Brown NL, Aghighi B, Entwistle MP, et al. Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc. 2013;20(3):526-34.

17. Seljan S, Baretic M, Kucis V. Information retrieval and terminology extraction in online resources for patients with diabetes. Coll Antropol. 2014;38(2):705- 10.

Trends in Novel Psychoactive Substance Use and the Impact of Irish Legislative Efforts

By Dr. Andrew Mazurek[1] , Dr. Margot Bolster[2]

Reviewed by Dr. André Toulouse[3]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of Pathology, University College Cork, Cork, Ireland

[3]Department of Anatomy and Neuroscience, School of Medicine, University College Cork, Cork, Ireland

Abstract

Introduction

Novel Psychoactive Substances (NPS) are emerging at increasingly rapid rates, creating unpredictability in drug markets and ineffective drug policies. Ireland has a drug-induced mortality rate greater than three times the European average and the highest rate of NPS use. Given the scarcity of published literature, the National Advisory Committee on Drugs has recommended trends in NPS use be studied in order to facilitate appropriate public health measures.

Objectives

To critically evaluate the published literature on NPS and establish the health risks associated with their use, trends in drug-induced fatalities, and the efficacy of legislative policies in reducing NPS consumption.

Methods

A systematic search of Medline and PubMed was completed based on pre-defined inclusion criteria, and relevant studies were selected for comprehensive analysis.

Results

Clinical experiences of NPS abusers predominantly involved neurological or psychological symptoms, coupled with cardiovascular effects. While the overall prevalence of NPS presentations in Europe remains low, fatal overdoses were primarily attributed to acute overdose and commonly involved ingestion of synthetic cathinones. Legislation in 2010 resulted in decreased rates of recent and problematic NPS use, along with higher rates of negative user experiences. No significant displacement towards established illicit drugs was reported.

Conclusion

This systematic review has demonstrated the current state of knowledge regarding NPS within an Irish context. The trends in NPS prevalence and toxicity are important considerations for the development of effective drug monitoring or enforcement strategies. This knowledge is further relevant for emergency physicians and forensic pathologists in order to make accurate medical assessments.

Introduction

The term novel psychoactive substance (NPS) encompasses those psychoactive substances not prohibited under the UN Convention on Narcotic Drugs, which are often designed to mimic the effects of illicit drugs[1]. To circumvent legal restrictions, they are often mislabeled as 'research chemicals', 'bath salts', or 'not fit for human consumption'[2]. NPS are emerging and being reformulated at increasingly rapid rates, creating unpredictability in drug markets and ineffective drug policies[1]. By 2016, the EU Early Warning System on New Psychoactive Substances was monitoring over 560 substances, with 70% emerging in the preceding five years[3]. The most commonly reported NPS are the synthetic cannabinoids (39.3%), synthetic cathinones (16.6%), and phenylethylamines (14.1%)[2].

The emergence of NPS in Ireland was noted in 2005 with the rise of 'legal highs' sold in headshops, which at the time complied with Irish law [4]. With their products rapidly gaining popularity, it was estimated that by 2010 the number of headshops had risen to one per 45,000 people. In response, the Irish government implemented two legislative controls in 2010 by i) amending the Misuse of Drugs Act to cover over 100 NPS, and ii) introducing the Criminal (Psychoactive Substances) Act[5]. While the regulations succeeded in curtailing the headshop supply route, availability through street and online markets has contributed to continued use of NPS among many users[4]. 'Darknet' cryptomarkets, encrypted networks isolated from the visible Internet, have particularly changed the model of illegal drug importation and distribution by utilizing anonymized transactions and delivery via legitimate couriers[6]. Research indicates a significant increase in online drug transactions in recent years, accounting for two-thirds of all darknet market activity[7].

In the "Youth Attitude on Drugs" report, Ireland was found to have the highest self-reported NPS use at 16% lifetime prevalence, whereas the majority of EU countries reported levels at or below 5%[8]. The national drug-induced mortality rate in adults was found to be 71 deaths per million in 2014, greater than three times the European average[9]. Current literature highlighting the specific contribution of NPS to drug fatalities, however, is limited mainly to case reports[10]. Despite anecdotal accounts, the published data on the effects and toxicity of NPS are scarce due the recent emergence of the phenomenon and the speed at which new compounds are formulated[11]. Expert concerns center on short term impacts such as paranoia and heightened aggression, injection-related bacterial infections, and particularly the deterioration of mental health in the form of suicidal ideation and acute psychosis[4]. In light of these findings, one of the key recommendations of the National Advisory Committee on Drugs is further research into the shifting patterns of drug consumption, with particular focus on the surveillance of local trends, the monitoring of online NPS sourcing, and the evaluation of harm reduction strategies[10-11]. These steps would contribute to a pragmatic public health approach, critical for the identification of emerging risks and development of appropriate evidence-based responses.

Methods

Electronic database searches were performed, using Medline (EBSCO) and PubMed, to identify published studies which address the objectives of the systematic review. The following search strategy was employed:

("Novel psychoactive substance" OR "new psychoactive substance" OR "legal high" OR "synthetic cathinone" OR "synthetic cannabinoid" OR "bath salts")

AND

(("Toxic*" OR "risk" OR "abuse" OR "fatal*" OR effect) OR (prevalence OR use) OR (legislat*)).

The keywords for NPS terminology were formulated based on reference to Hohmann et al.[2], given the lack of consistency in the terms used by researchers, lawmakers, and drug users.

When evaluating studies regarding the trends in NPS prevalence and response to legislation, this review aimed to retrieve research in the context of the Irish population as these parameters are highly influenced by local settings, NPS access, and demographic variables[1]. Given the limited nature of research overall in this field[10], this priority may not be achieved and literature involving international settings with strong research methodology will be selected in these cases. Indeed, the terms "Irish" or "Ireland" were not included in the search strategy as this severely limited the results retrieved when initially attempted. The preference of Irish settings for studies pertaining to the adverse effects of NPS will not be applied as rigorously given that adverse drug reactions are less prone to these national influences[12]. Additionally, literature studying larger NPS drug categories will be preferentially selected over studies involving specific single drugs.

This review will seek to select studies with strong research methodologies to provide a more solid foundation on which to appraise the current state of knowledge. Unfortunately, it has been reported that information on NPS primarily originates from case reports and case series[13], but these will not be selected where more suitable research is retrieved. Based on the rapid rate of reformulation of NPS, recent literature is preferable but a timeframe of 2010-2019 will be employed in the search strategy since 2010 represents the introduction of Irish NPS legislation, and studies shortly following this timeframe may be important for analyzing the impact of regulation on NPS consumption. Based upon the criteria outlined, inclusion and exclusion criteria for screening articles were defined.

Inclusion Criteria	Exclusion Criteria
- Original research article - Research aims involving NPS toxicity, use or prevalence, fatalities, or legislation - Published between 2010-2019 - English language - Available as free full text - Human studies - Study population representative of the general population or active NPS users - Studies on NPS drug categories (in preference over single drug studies; if available)	- Case reports or case series - Systematic or narrative reviews - Meta-analyses or evidence summaries - Governmental or organizational publications - Conference proceedings - Animal studies - Solely toxicological analysis - Solely paediatric population - Population not reflective of general population (i.e. solely prison population, solely psychiatric patients)

Application of these inclusion and exclusion criteria to the initial results obtained in PubMed and Medline (EBSCO) resulted in 361 studies screened through title or abstract, followed by 35 full text articles reviewed for eligibility, after which 10 articles were included in the systematic review (Figure 1).

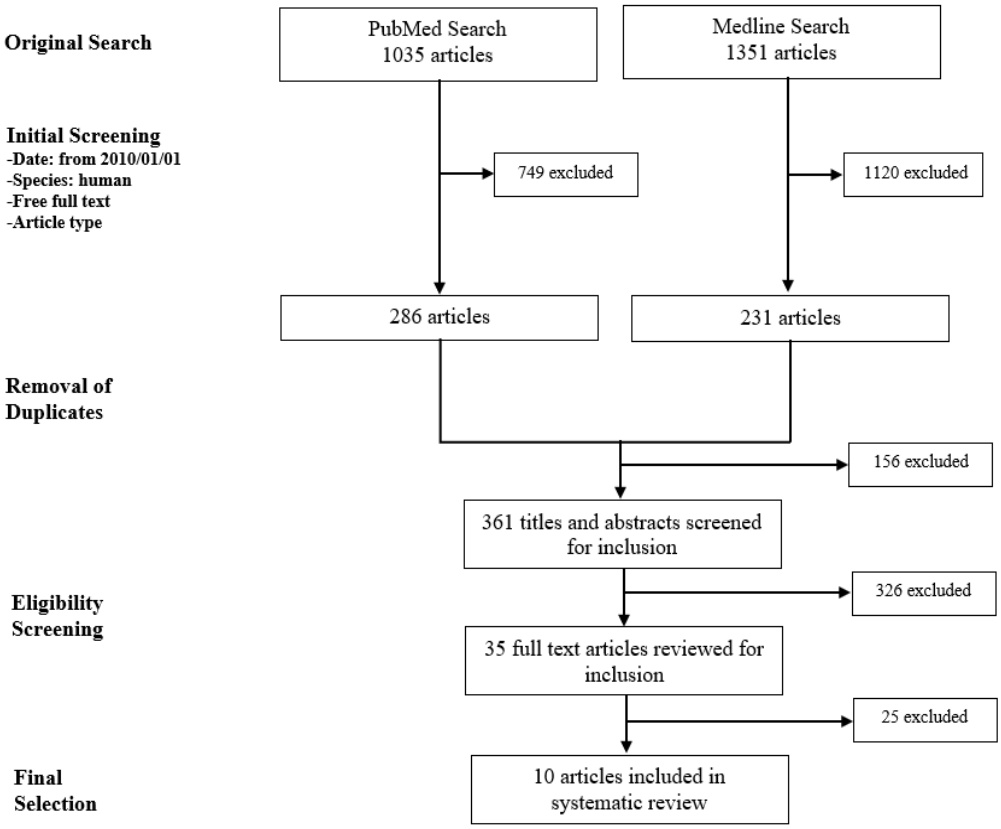
Results

Toxicity Associated with NPS Consumption

The clinical experience and demographic characteristics associated with NPS toxicity were analyzed in three multicenter surveys[14-16] and an epidemiological case-control study[17] (Table 2). While a population survey within Ireland was not obtained, the demographic profile of users reporting acute toxicity was highly concordant among the surveys despite large geographic and societal variation (Netherlands[14], Japan [15], and US[16]). The majority of NPS abusers across studies were male (>75%) and less than 30 years old. Clinical symptoms reported on admission were predominantly neurological and psychological, with high levels of agitation, hallucination, confusion, and nausea[14-16]. Cardiovascular symptoms often presented during acute toxicities, with tachycardia and hypertension consistently identified across the studies and reflective of published literature in other jurisdictions[18]. Mechanisms of action for most NPS remain uncertain, however the sympathomimetic syndrome has been proposed for many NPS categories, particularly synthetic cathinones [16]. Inhibition of membrane catecholamine transporters is suspected to result in reuptake inhibition, and initial animal studies concur[19]. Further complications to acute toxicities occurred in the form of major organ complications (i.e. liver injury, rhabdomyolysis) and harmful behaviours (i.e. suicide attempts, traffic accidents)[15-16]. Importantly, the severity of adverse effects and harmful behaviours was noted to increase with time and prolonged consumption[15].

The epidemiological study focused on one particular health risk, HIV infection, however was included as it represented a vulnerable population specific to Ireland[17]. Prompted by an

Figure 1
Study Identification and Selection.



outbreak identified by the Department of Public Health, the study provided the first evidence of an association between HIV in the homeless and injection of a synthetic cathinone, 'snow blow'. Higher risk scores were associated with females, chaotic drug users, daily injectors, and multiple NPS consumption[17].

Trends in NPS Prevalence and Fatal Cases

Observed patterns in NPS consumption were assessed through cross-sectional database analyses[20-21] and retrospective forensic casework studies[22-23] (Table 2). Reporting from 16 European monitoring centres, including two Irish districts, demonstrated low overall prevalence of NPS in drug-related emergency presentations, between 0-2.8% monthly, with higher frequencies for traditional recreational drugs or misused prescription medicines[21]. The most frequently reported NPS in European users were synthetic cathinones, particularly mephedrone and methedrone. The Australian database, in contrast, found a shift in most reported drug from mephedrone in 2010 to 2C-x phenylethylamines in 2013, demonstrating volatility of drug markets and the influence of local factors on drug consumption[20]. NPS users were more likely to source drugs through online markets, which has been corroborated elsewhere and believed to reflect preferences for avoiding threats of violence[24]. NPS users were further associated with younger age of first drug use, higher consumption frequency, and perceptions of traditional street drugs as lower quality[20]. These individual characteristics may be key factors in users' decisions to continue or increase NPS consumption.

Regarding fatal NPS cases, the leading cause of death reported in forensic casework studies was acute drug toxicity, particularly with synthetic cathinones[22-23]. Knowledge regarding the pathophysiology of these adverse events, however, is severely constrained. Pathological findings commonly reported were cardiac ischaemia and cerebral hypoxia[21,23], which may be explained by chronic vasoconstriction elicited by NPS, leading to artery stenosis[25]. Traumatic injuries are also important contributors to NPS fatalities, with relative high prevalence of fatal hangings, mechanical suicide (i.e. asphyxia, falls), and homicide[22]. Post-mortem drug

concentrations varied widely, prohibiting the establishment of 'fatal ranges' for commonly encountered NPS.

Efficacy of Legislation in NPS Regulation

The changes to NPS use and accessibility following Irish legislation in 2010 were assessed through a cross-sectional[26] and qualitative study[27] (Table 2). While significant changes to lifetime prevalence were not detected post-legislation, this period demonstrated lower rates of recent NPS use and decreased problematic practices[26]. Such reductions are consistent with short-term results following similar bans in other countries[28-29]. While use of all NPS categories remains higher than desired by legislators and health advocates, the research has found that post-ban polydrug use fell among NPS users and there was no large displacement towards established illegal drugs as some expected[26].

In parallel, the qualitative study revealed that mephedrone users in the post-legislative timeframe noticed shifts in their 'high' experiences[27]. 'New' negative effects with continued mephedrone use were noticed, commonly described as more serious mood changes, depression, or anger. During interviews, participants did not link the legislative controls and media reporting to their decreased NPS use, yet their attitudes toward the safety and perceived health risks of these substances became more critical. These changes were often attributed to negative personal or peer experiences[27], however the influence of these public health initiatives should be critically assessed. Concerns also grew among users about potential contaminants and mixed agents following legislation, given the need to utilize street markets. Corresponding with these user considerations, other small-scale post-legislative studies in Ireland report reductions in various NPS detection rates[30-31]. Despite the limited scope of the qualitative study, it provides insight into the perceptions of NPS users following changes to drug accessibility, important for the development of future legislative proposals.

Discussion

The analysis of ten original research articles has provided insight into the current state of the literature regarding novel psychoactive substances. Despite variability in the geographic context of the studies, the clinical experiences of NPS abusers were consistent with predominant neurological or psychological symptoms, coupled with cardiovascular effects of tachycardia and hypertension[14-16]. The mechanism remains unclear for most drugs, but the studies and further literature support the sympathomimetic syndrome[2,19]. This knowledge is important in application to emergency physicians, where recognition of the syndrome despite negative drug screens can help with faster delivery of appropriate care. Similarly, associations of toxicity with major organ complication and harmful self-behaviours[15-16] should be considered when evaluating patient risk and therapies. Population surveys are common in this research area, most likely due to feasibility, however their application is accompanied by certain limitations. Marginalized populations, such as the homeless, prisoners, or youth, are often underrepresented in such surveys[1]. The health risks to which NPS users are exposed will remain a difficult topic of research given the inherent subjectivity of drug effects, the lack of information about NPS interactions with other illicit substances, the lack of certainty in contents of drugs consumed, and rapid altering of NPS molecular structures to bypass regulation constantly setting researchers behind[13].

Research in a European context has revealed low overall prevalence of NPS in emergency presentations, averaging 1%[21]. The most frequently reported were the synthetic cathinones, however volatility of these preferences in time and space was noted[20]. The associations of NPS users with younger age of first drug use, greater frequency of consumption, and preference for online markets[20,24] are important considerations when tailoring prevention and rehabilitation programs. Frequent involvement of synthetic cathinones in fatal cases reveals the necessity to keep toxicological screens updated

for these compounds to facilitate accurate pathological determinations. There is also need for pathologists to be aware of the common findings of ischaemia and cerebral hypoxia [21,23] when assessing suspected cases.

A major source of information on NPS prevalence is found in non-scientific publications such as governmental or agency reports[32-34], which were not included per systematic review methodology. These publications provide population-wide data at regular intervals, important for tracking the implementation of national health strategies, but in turn avoid important peer-review processes. Certain researchers bypass these processes due to the lengthy processing times, preferring to quickly disseminate to the general public. Scientific publications of survey studies can often suffer from small sample sizes, self-reporting errors, and memory biases[14]. Whether assessing normal use or fatal events, it is recommended that information on NPS be triangulated from all relevant sources[7], which may include emergency departments, forensic institutions, and poison control centres[14]. In forensic cases, the influence of post-mortem redistribution is particularly important when determining the contribution of drugs to death[35-36].

The 2010 regulations were associated with decreased rates of recent and problematic NPS use[26], which is consistent with data from other countries[28-29]. Importantly there was not a significant displacement towards established illegal narcotics. In terms of user perceptions, users noticed greater rates of negative effects with continued use[27], which may reflect effective public health initiatives or rise of potential contaminants in altered drug markets. Criticism of NPS bans without supplementary measures has been raised, as evidence of small reductions does not necessarily indicate that easy access to these drugs has been negated[37-38]. Current research does not provide rationale for Ireland to alter the current prohibitionist approach[26], but an important negative consequence is that compounds which became controlled limited academic research given the burdens of licensing requirements[39]. It is recommended provisions for research be provided in future legislation.

Conclusion

The issue of NPS is a major concern for governments across Europe, therefore knowledge of the trends in their prevalence and toxicity are important considerations for the development of effective drug monitoring or enforcement strategies. The synthesis of this information is further necessary for emergency physicians and forensic pathologists to make accurate clinical judgements.

This literature review has demonstrated that clinical experiences of NPS abusers are consistent despite geographic variability, however the mechanisms underlying these adverse effects remain unclear. Despite low overall prevalence of NPS use across the continent, the association of synthetic cathinones with fatal overdose remains a concerning trend in the published data. Meanwhile, legislation implemented by the Irish government has resulted in decreased rates of problematic use without significant displacement towards other illegal narcotics.

This review is limited by the exclusion of case reports and governmental publications, which produce meaningful insights into NPS trends but do suffer from a lack of strong research methodology. The rapid reformulation of these substances, inherent to current drug markets, creates challenges in keeping literature updated and relevant. High levels of polysubstance use are a confounding variable in the studies cited as the determination of specific agents contributing to death is impeded. Lastly, the prevalence of NPS in fatalities may be underrepresented as post-mortem toxicology for every autopsy is not currently feasible.

Allowing for these limitations, this review is nonetheless able to provide a comprehensive overview of the public health issues surrounding novel psychoactive substances. Given the scarcity of systematic data, the authors agree with

recommendations to develop a centralized national database for the collection of emergency department data[11]. The insights provided by such a database would aid public health agencies to understand the harm caused by existing and newly developed substances. The authors further recommend that future research in this field focus on the analysis of recent trends in drug fatalities within an Irish context. Such data will provide a better understanding of the vulnerable populations and specific health risks unique to this demographic population, enhancing efforts to implement appropriate and proactive harm-reduction strategies.

References

1. O'Neill C. Novel psychoactive substances: risks and harms. Community Pract. 2014 Aug;87(8):45-7.

2. Hohmann N, Mikus G, Czock D. Effects and risks associated with novel psychoactive substances: Mislabeling and sale as bath salts, spice, and research chemicals. Dtsch Arztebl Int. 2014 Feb;111 (9):139-47.

3. Corazza O, Parrott AC, Demetrovics Z. Novel psychoactive substances: Shedding new lights on the ever-changing drug scenario and the associated health risks. Hum Psychopharmacol. 2017 May;32(3):e2616.

4. Van Hout MC. The Dynamic Landscape of Novel Psychoactive Substance (NPS) Use in Ireland: Results from an Expert Consultation. Int J Ment Health Addiction. 2017 Oct;15(5):985-92.

5. Ryall G, Butler S. The great Irish head shop controversy. Drugs: Educ Prev Polic. 2011 Aug;18(4):303-11.

6. Pergolizzi JV, LeQuang JA, Taylor R, Raffa RB. The "Darknet": The new street for street drugs. J Clin Pharm Ther. 2017 Dec;42 (6):790-2.

7. European Monitoring Centre for Drugs and Drug Addiction and Europol. Drugs and the darknet: Perspectives for enforcement, research and policy. Luxembourg: EMCDDA–Europol Joint Publications, 2017.

8. The Gallup Organization. Youth attitudes on drugs. Luxembourg: European Commission, 2011.

9. European Monitoring Centre for Drugs and Drug Addiction. Ireland: Country Drug Report 2017. Luxembourg: Publications Office of the European Union, 2017.

10. Hearne E, Wells J, Van Hout MC. Country report on New Psychoactive Substances in Ireland. Waterford: NPS-Transnational Project, 2017.

11. Kelleher C, Christie R, Lalor K, Fox J, Bowden M, O'Donnell C. An overview of new psychoactive substances and the outlets supplying them. Dublin: National Advisory Committee on Drugs, 2011.

12. Martins SS, Sampson L, Cerdá M, Galea S. Worldwide prevalence and trends in unintentional drug overdose: A systematic review of the literature. Am J Public Health. 2015 Nov;105(11):e29–e49.

13. Tracy DK, Wood DM, Baumeister D. Novel psychoactive substances: types, mechanisms of action, and effects. BMJ. 2017 Jan 25;356:i6848.

14. Hondebrink L, Nugteren-van Lonkhuyzen JJ, Van Der Gouwe D, Brunt TM. Monitoring new psychoactive substances (NPS) in The Netherlands: data from the drug market and the Poisons Information Centre. Drug Alcohol Depend. 2015 Feb;147:109-15.

15. Kamijo Y, Takai M, Fujita Y, Sakamoto T. A multicenter retrospective survey of poisoning after consumption of products containing novel psychoactive substances from 2013 to 2014 in Japan. Am J Drug Alcohol Abuse. 2016 Sep;42(5):513-9.

16. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. Clin Toxicol. 2011 Jul;49(6):499-505.

17. Giese C, Igoe D, Gibbons Z, Hurley C, Stokes S, McNamara S, et al. Injection of new psychoactive substance snow blow associated with recently acquired HIV infections among homeless people who inject drugs in Dublin, Ireland, 2015. Euro Surveill. 2015;20(40): 30036.

18. Murray DB, Potts S, Haxton C, Jackson G, Sandilands EA, Ramsey J, et al. 'Ivory wave' toxicity in recreational drug users; integration of clinical and poisons information services to manage legal high poisoning. Clin Toxicol. 2012 Feb;50(2):108-13.

19. Nagai F, Nonaka R, Satoh Hisashi Kamimura K. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. Eur J Pharmacol. 2007 Mar 22;559(2-3):132-7.

20. Burns L, Roxburgh A, Matthews A, Bruno R, Lenton S, Van Buskirk J. The rise of new psychoactive substance use in Australia. Drug Test Anal. 2014 Jul-Aug;6(7-8):846-9.

21. Dines AM, Wood DM, Yates C, Heyerdahl F, Hovda KE, Giraudon I, et al. Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). Clin Toxicol. 2015 Oct;53(9):893-900.

22. Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. Forensic Sci Int. 2014 Oct;243:55-60.

23. Ezaki J, Ro A, Hasegawa M, Kibayashi K. Fatal overdose from synthetic cannabinoids and cathinones in Japan: demographics and autopsy findings. Am J Drug Alcohol Abuse. 2016 Sep;42 (5):520-9.

24. Barratt MJ, Ferris JA, Winstock AR. Safer scoring? Cryptomarkets, social supply and drug market violence. Int J Drug Policy. 2016 Sep;35:24-31.

25. Suzuki H, Kawai S, Aizawa T, Kato K, Sunayama S, Okada R, Yamaguchi H. Histological evaluation of coronary plaque in patients with variant angina: relationship between vasospasm and neointimal hyperplasia in primary coronary lesions. J Am Coll Cardiol. 1999 Jan;33 (1):198-205.

26. Smyth BP, James P, Cullen W, Darker C. "So prohibition can work?" Changes in use of novel psychoactive substances among adolescents attending a drug and alcohol treatment service following a legislative ban. Int J Drug Policy. 2015 Sep;26(9):887 -9.

27. Van Hout MC, Brennan R. Curiosity killed M-Cat: A post-legislative study on mephedrone use in Ireland. Drugs: Educ Prev Pol. 2012;19(2):156-62.

28. Loeffler G, Craig C. The effect of legal bans on poison control center contacts regarding 'legal highs'. Addiction. 2013 Jul;108 (7):1348-9.

29. Wilkins C, Sweetsur P. The impact of the prohibition of benzylpiperazine (BZP) 'legal highs' on the prevalence of BZP, new legal highs and other drug use in New Zealand. Drug Alcohol Depend. 2013 Jan 1;127(1-3):72-80.

30. O'Byrne PM, Kavanagh PV, McNamara SM, Stokes SM. Screening of stimulants including designer drugs in urine using a liquid chromatography tandem mass spectrometry system. J Anal Toxicol. 2013 Mar;37(2):64-73.

31. Van Hout MC, Bingham T. "A costly turn on": patterns of use and perceived consequences of mephedrone based head shop products amongst Irish injectors. Int J Drug Policy. 2012 May;23 (3):188-97.

32. EMCDDA. New psychoactive substances in Europe: An update from the EU Early Warning System. March 2015, Luxembourg: Publications Office of the European Union.

33. European Commission. Youth attitude on drugs. 2011, Brussels: European Commission.

34. Health Research Board. Drug-related deaths and deaths among drug users in Ireland. 2013 figures from the National Drug-Related Deaths Index. 2015, Dublin: Health Research Board.

35. Yarema MC, Becker CE. Key concepts in postmortem drug redistribution. Clin Toxicol. 2005:43:235-41.

36. Han E, Kim E, Hong H, Jeong S, Kim J, In S, Chung H, Lee S. Evaluation of postmortem redistribution phenomena for commonly encountered drugs. Forensic Sci Int. 2012;219:265-71.

37. McElrath K, O'Neill C. Experiences with mephedrone pre- and post-legislative controls: Perceptions of safety and sources of supply. Int J Drug Policy. 2011;22:120-7.

38. Measham F, Wood DM, Dargan PI, Moore K. The rise in legal highs: Prevalence and patterns in the use of illegal drugs and first- and second-generation 'legal highs' in South London gay dance clubs. J Subst Use. 2011;16:263-72.

39. Kavanagh P, Power JD. New psychoactive substances legislation in Ireland – perspectives from academia. Drug Testing Anal. 2014;6(7–8):884-891.

[This page has been intentionally left blank. Please turn over.]

Calprotectin as a Marker

of Disease Activity In Spondyloarthritis

By Ioana Tereza Florica[1] , Dr. Sinead Harney[2]

Reviewed by Dr. André Toulouse[3]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of Rheumatology, Cork University Hospital, Cork, Ireland

[3]Department of Anatomy and Neuroscience, School of Medicine, University College Cork, Cork, Ireland

Abstract

Introduction

Spondyloarthritis is a group of arthritic diseases that classically manifest as inflammation of the sacroiliac and limb joints, as well as the axial skeleton. Microscopic bowel inflammation is identifiable in over 50% of these patients. Calprotectin measured in the serum and stool is an emerging surrogate marker of disease activity and/or bowel inflammation in spondyloarthritis.

Objective

This article aims to review published literature to determine the accuracy of serum and faecal calprotectin levels for use in monitoring bowel inflammation and spondyloarthritis disease activity.

Methods

Boolean operator strategy was used to search two databases (Embase and PubMed) and 52 relevant articles were identified. Duplicate results were eliminated, inclusion and exclusion criteria were applied.

Results

Ten studies met the inclusion criteria and were summarized and analyzed. The EBL Validity questionnaire was applied to determine study quality. All research articles found calprotectin to be elevated in spondyloarthritis patients when compared to controls. Faecal calprotectin was superior in detecting disease activity and correlated with disease activity questionnaires, radiology and endoscopy results. Only one study assessed the effect of treatment on calprotectin and its correlation to bowel inflammation.

Conclusion

Faecal calprotectin shows promise as a surrogate marker for disease activity and bowel inflammation in spondyloarthritis. Future studies should focus on the effect of treatment on faecal calprotectin and whether some treatments are better at preventing the progression of bowel inflammation in addition to treating spondyloarthritis. Supplementary investigations are needed to identify whether faecal calprotectin is useful as a marker of disease activity in response to treatment.

Keywords

Spondyloarthritis, SpA, Disease Activity, Calprotectin, Bowel Inflammation

Introduction

Spondyloarthritis

Spondyloarthritis (SpA) encompasses several arthritic diseases: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, and SpA with inflammatory bowel disease [1]. These diseases are grouped by similarities in pathophysiology; characteristically: progressive inflammation and structural joint damage. Clinical manifestations are common in: entheses, sacroiliac joints, and the axial skeleton. Extra-articular sites include: the gut, skin, eyes and aortic valve [1]. These diseases affect roughly 1% of the adult population [2], predominantly males. Though only a small portion of the population positive for the HLA-B27 haplotype develop spondyloarthritis, this genetic marker is in part responsible for genetic susceptibility [3] .

Bowel Inflammation

Over 50% of SpA patients have histopathology consistent with bowel inflammation in the absence of gastrointestinal symptoms [3]. The degree of bowel inflammation may be a marker of disease prognosis as it is associated with bone marrow oedema in sacroiliac joints and disease progression [4, 5]. Bowel inflammation is classically measured via colonoscopy. However, it is an expensive, invasive and unpleasant procedure. Calprotectin is emerging as a surrogate marker.

Calprotectin

Calprotectin is a pro-inflammatory calcium-binding protein released from monocytes and granulocytes [6]. Calprotectin levels are measurable in the stool and rise with increased bowel inflammation [7]. Often, faecal calprotectin (FC) is used to diagnose and monitor treatment in patients with inflammatory bowel disease (IBD) [7]. Alternatively, calprotectin can also be tested in the serum and is a useful marker of disease activity and joint inflammation in rheumatoid arthritis [8].

Inclusion	Exclusion
• Adults only (18 years plus) • English • 2010-2020 • Human only subjects • Full Text Access • Articles focusing on any/all Spondyloarthritis subtype(s)	• Inflammatory bowel disease as the primary disease • Focus on other rheumatic diseases • Any articles without original research (i.e. Review articles) • Conference Abstracts

Table 1: Inclusion and Exclusion Criteria

In the past decade, calprotectin in the stool and serum has been explored as a possible marker of disease activity in patients with spondyloarthritis. Microscopic bowel inflammation in SpA patients occurs without gastrointestinal symptoms and may eventually develop into Crohn's disease. Minimizing the chances of disease progression in spondyloarthritis is reliant on an accurate and accessible marker of disease activity.

Objectives

1) To determine the efficacy of serum and faecal calprotectin in detecting subclinical bowel involvement in patients with Spondyloarthritis.

2) To determine if serum and/or faecal calprotectin are suitable markers of disease activity in spondyloarthritis.

Methods

Two databases were searched (Embase and PubMed). The inclusion and exclusion criteria are presented in Table 1. In total, 10 papers met the criteria, were included in the literature review, and are summarized in Table 2. To outline article quality, the EBL Validity questionnaire was applied to all articles and validity scores calculated (Table 4).

Primary Search

The initial search was conducted using Embase (Figure 1). The search made use of Boolean operators to structure results. The search strategy was: (spondylarthritis OR spondyloarthropathy OR spondyloarthritis OR SpA) AND (gastrointestinal OR digestive OR gut OR enteropathy OR intestine OR gi OR bowel) AND (calprotectin OR calprotectin test kit OR calprotectin elisa kit). This yielded 32 articles. Narrowing by human subjects only, adults and published 2010-2020, reduced the results to 16. Limiting to articles only, removed 12 con-

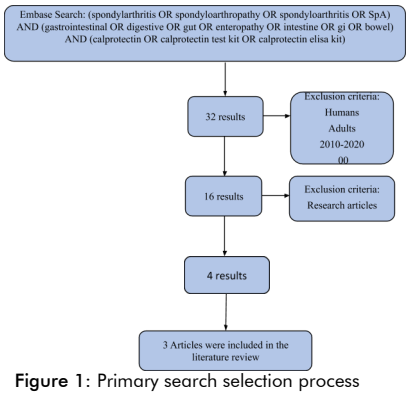


Figure 1: Primary search selection process

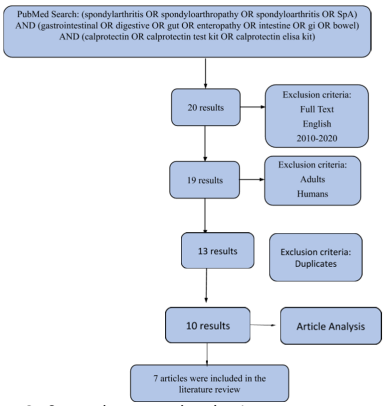


Figure 2: Secondary search selection process

ference abstracts. One did not meet inclusion criteria after article analysis. Three articles were included in the literature review. The selection strategy is visualised in Figure 1.

Secondary Search

The secondary search was conducted using PubMed (Figure 2). The same search strategy was repeated. This yielded 20 results. Narrowing the results to full text, English results published 2010-2020, left 19 articles. Further narrowing by adults and humans yielded 13 articles. Any duplicate articles that were selected through the Embase database were removed. After article analysis, only 7 articles met the inclusion criteria and were included. The selection strategy is visualized in Figure 2.

Results

Abbreviations used:

Anti-TNFα: anti- Tumour Necrosis Factor alpha

Anti-TTG: Anti-tissue Transglutaminase Antibody

AS: Ankylosing Spondylitis

ASDAS: Ankylosing Spondylitis Disease Activity Score

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BAS-G: Bath Ankylosing Global Score

BASMI: Bath Ankylosing Metrology Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

CBC: Complete blood count

CD: Crohn's Disease

CRP: C-reactive protein

DM: Diabetes Mellitus

ESR: Erythrocyte sedimentation rate

fCAL/FC: Faecal calprotectin

GI: Gastrointestinal

Hb: Haemoglobin count

HBI: Harvey- Bradshaw index

IBD: Inflammatory Bowel Disease

MRI: Magnetic Resonance Imaging

NSAID: Non-steroidal Anti-inflammatory Drugs

PLT: Platelet Count

QOL: Quality of Life

RA: Rheumatoid Arthritis

SI joints: Sacroiliac Joints

SpA: Spondyloarthritis

WBC: White blood cell count

Calprotectin and Disease Activity Questionnaires

All studies identified calprotectin to be significantly increased in patients with SpA. Only five articles reported a correlation with disease activity [9,10,12,14,17] as measured by validated disease activity questionnaires: BASDAI and ASDAS [18]. The studies had diverging results as some found a correlation between FC and ASDAS but not BASDAI [9] while another found a correlation with BASDAI/ BASFI [12]. One study found a correlation between FC and both ASDAS and BASFI [17] while another failed to correlate serum calprotectin with any of the disease activity questionnaires [11]. Higher fecal calprotectin levels and higher scores on BASDAI and BASFI were identified in patients who were subsequently diagnosed with co-morbid Crohn's Disease [15]. In a longitudinal study [14], a higher FC at baseline was correlated with increased disease activity on all questionnaires at a 5-year follow-up assessment.

Calprotectin and Radiology

Patients with higher FC levels have significantly more radiographic inflammatory lesions in the sacroiliac joints [16, 17].

Calprotectin and Bowel Inflammation

Those with higher FC are more likely to test positive for IBD related serology [10]. This is present in the absence of GI symptoms [9,12]. Higher serum and stool calprotectin are present in those with microscopic bowel inflammation, irrespective of CRP [6]. High FC and the presence of diarrhea with mucous are the best pre-

dictors of subsequent diagnosis with IBD [14].

FC was found to be correlated with histologically chronic inflammation of the bowels, while serum calprotectin was associated with acute inflammation [6]. A long-term study found development of bowel inflammation in 7.4% of patients tested with ileocolonoscopy at 5-year follow-up [14]. Capsule Endoscopy reveals higher FC levels to be better correlated with inflammation localized to the colon [15]. In patients with high FC, 80% had recognizable bowel lesions while only one patient with normal FC had bowel lesions [16].

Serum versus Faecal calprotectin

Two studies measured serum calprotectin [11,13], four measured faecal calprotectin [10,15,16,17] and four measured both [9,6,12,14]. Serum calprotectin was found to be higher in patients [11,13] when comparing to controls but failed to identify patients on an individual level [13]. When measured together, faecal calprotectin was superior in measuring disease activity. Two studies found faecal calprotectin to be increased in SpA patients while serum calprotectin was not [9,12]. One study found serum calprotectin to be positively correlated with faecal calprotectin but failed to identify it as a predictor of IBD diagnosis [14].

The effect of treatment

Frequent NSAID use was correlated with a higher FC, but occasional or rare use was not [9]. Patients with higher FC at baseline were found to have a better treatment response to anti-TNF alpha therapy [16].

Discussion

Disease Activity

This review aimed to discern the accuracy of serum and faecal calprotectin in reporting disease activity and/or bowel inflammation in spondyloarthritis (SpA). All studies identified calprotectin levels to be a significantly increased in patients with SpA. Faecal calprotectin was more effective than serum calprotectin at detecting disease activity. The bowel is close to the main sites of involvement in SpA, the sacroiliac joints and axial spine. Thus, the inflammation of the bowel may be due to an increase in circulating inflammatory mediators attacking vulnerable proximal tissue.

Serum calprotectin is a non-specific measure of inflammation. High levels are associated with various inflammatory processes: complications with organ transplants [19], early stages of pulmonary diseases [20] and rheumatoid arthritis [8], and may be deceptively negative in neutropenic patients [21]. Literature relating serum calprotectin levels to spondyloarthritis is limited. Articles included in this review did not conclusively agree that serum calprotectin used in isolation is a robust marker for disease activity.

Of the studies included, half studied patients with ankylosing spondylitis (AS) only. AS classically affects the sacroiliac joints and axial spine. In severe cases, the intervertebral discs calcify, the joint spaces narrow and this can lead to fusion of the facet joints, termed - "bamboo spine" [22]. Two studies in these patients [9,12] found a significantly higher faecal calprotectin when compared to controls but no difference in serum calprotectin. It is possible that axial symptoms in these patients contribute to inflammation of the bowel but not diffuse inflammation.

Since many different validated disease activity questionnaires exist to assess spondyloarthritis, there was some variation in correlations of calprotectin and disease activity. However, all but one study [11] using any disease activity questionnaire found a positive correlation between calprotectin and disease activity. It is important to note; the study in question had a small sample size (N=31) and only collected blood samples from AS patients. Another study [6] suggests serum calprotectin is better correlated with acute rather than chronic inflammation. It is possible, participants were long-term patients and thus well treated, minimizing serum calprotectin.

Bowel Inflammation

Studies using radiographic imaging or endoscopy found an association between faecal calpro-

tectin and disease activity. Patients with high faecal calprotectin were highly likely to have bowel lesions and increased risk of progression to inflammatory bowel disease. However, some studies [9,14,16] had target levels for faecal calprotectin in order to perform ileocolonoscopy. Since only patients with higher local inflammation provided histological samples it is possible that results were skewed. Nevertheless, studies that performed some sort of endoscopy on all patients [6,15,16], regardless of faecal calprotectin level, found similar significant results associating bowel inflammation severity to faecal calprotectin. Overall, faecal calprotectin was affective in detecting bowel inflammation, correlating to disease activity and providing a prognosis for the development of disease.

Effect of Treatment

NSAIDs utilized prior to sample collection can increase faecal calprotectin [23]. However, only five of studies [9,10,14,15,16] accounted for this via analysis of results or exclusion criteria. Though most studies found a positive relationship between faecal calprotectin and SpA patients, this may be in part, due to NSAID use. One study investigated the effect of TNF-alpha inhibitors. Participants with higher faecal calprotectin prior to the commencement of treatment, had a better treatment response. It is important to note that, Adalimumab, the TNF-alpha inhibitor used in the study, is also used to treat inflammatory bowel disease (IBD) [24]. Thus, the possibility cannot be excluded that these patients had some early changes consistent with IBD that the drug may have masked.

Quality of Studies

Most studies included were of reasonably high quality (64-95% validity). A recurring issue was the lack of inclusion of questionnaires in publication as well as appropriate description of physical assessments. Many participants were also patients receiving follow-up assessments of their illness, it was often unclear whether the individual performing the medical assessment was the same as the researcher. Sample sizes also varied due to the use of pre-existing cohorts in comparison to seeking participants for the current project only. Overall, studies were simple and well analyzed and thus, their results externally valid.

Study heterogeneity

The literature examined in this review were highly variable, limiting comparability. The study focus differed amongst the articles. The availability of participants is the likely reason why five articles studied AS only [9]. Though there was overlap in measures used to quantify disease, some studies did not include radiology and/or endoscopy. Thus, the reliability of measurement is reduced to that of surrogate markers. Furthermore, there was variation in the criteria used to diagnose disease. Some studies used the modified New York Criteria, others used ICD-10 and the rest relied on the European Spondyloarthropathy Study Group criteria. The exclusion criteria were not unanimous throughout all studies as some studies addressed many confounding variables and comorbidities while others did not.

Limitations

All articles were published in the last 8 years and one article was included that was published online ahead of print [16]. It is possible that new articles may have been published since the original database search or may appear in the near future. Only free full text English articles were included in this review. One study was not available through the University College Cork library and was accessed via another university's library. This review involved only one author and is susceptible to selection bias and human error.

Future studies

Future studies should seek to understand the practicality of faecal calprotectin in monitoring disease activity in response to treatment. Only one published study investigated the effect of one drug, a TNF-α inhibitor. Spondyloarthritis patients could be using many types of treatment including: NSAIDs, disease modifying anti-inflammatory agents, and corticosteroids [25]. Since bowel inflammation is prevalent in more than 50% of SpA patients [3], research must explore the effect of these treatments on bowel

inflammation to identify drugs that are superior in treating SpA, while preventing the progression of bowel disease.

Conclusion

Spondyloarthropathies are progressive diseases with adverse effects on quality of life, directly associated with disease activity [26]. Increased disease activity is also associated with risk of subsequent diagnosis of bowel disease. Many markers of disease activity exist but involve expensive and invasive procedures. This literature review suggests the use of faecal calprotectin as an effective surrogate marker for bowel inflammation and disease activity in spondyloarthritis patients. Additional studies are necessary to investigate the effect of treatment on faecal calprotectin and bowel inflammation.

References

1. Khan MA. Update on spondyloarthropathies. Annals Of Internal Medicine. 2002;136(12):896-907.

2. Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. N Engl J Med. 2016;374(26):2563-74.

3. Cuvelier C, Barbatis C, Mielants H, De Vos M, Roels H, Veys E. Histopathology of intestinal inflammation related to reactive arthritis. Gut. 1987;28(4):394-401.

4. De Vos M, Mielants H, Cuvelier C, Elewaut A, Veys E. Long-term evolution of gut inflammation in patients with spondyloarthropathy. Gastroenterology. 1996;110(6):1696-703.

5. Van Praet L, Jans L, Carron P, Jacques P, Glorieus E, Colman R, et al. Degree of bone marrow oedema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort. Ann Rheum Dis. 2014;73(6):1186-9.

6. Cypers H, Varkas G, Beeckman S, Debusschere K, Vogl T, Roth J, et al. Elevated calprotectin levels reveal bowel inflammation in spondyloarthritis. Ann Rheum Dis. 2016;75(7):1357-62.

7. D'Angelo F, Felley C, Frossard JL. Calprotectin in Daily Practice: Where Do We Stand in 2017? Digestion. 2017;95(4):293-301.

8. Madland TM, Hordvik M, Haga HJ, Jonsson R, Brun JG. Leukocyte protein calprotectin and outcome in rheumatoid arthritis. A longitudinal study. Scand J Rheumatol. 2002;31(6):351-4.

9. Klingberg E, Carlsten H, Hilme E, Hedberg M, Forsblad-d'Elia H. Calprotectin in ankylosing spondylitis--frequently elevated in feces, but normal in serum. Scand J Gastroenterol. 2012;47(4):435-44.

10. Matzkies FG, Targan SR, Berel D, Landers CJ, Reveille JD, McGovern DP, et al. Markers of intestinal inflammation in patients with ankylosing spondylitis: a pilot study. Arthritis Res Ther. 2012;14(6):R261.

11. Oktayoglu P, Bozkurt M, Mete N, Caglayan M, Em S, Nas K, et al. Elevated serum levels of calprotectin (myeloid-related protein 8/14) in patients with ankylosing spondylitis and its association with disease activity and quality of life Markers of intestinal inflammation in patients with ankylosing spondylitis: a pilot study. J Investig Med. 2014;62(6):880-4.

12. Duran A, Kobak S, Sen N, Aktakka S, Atabay T, Orman M. Fecal calprotectin is associated with disease activity in patients with ankylosing spondylitis. Bosn J Basic Med Sci. 2016;16(1):71-4.

13. Turina MC, Yeremenko N, van Gaalen F, van Oosterhout M, Berg IJ, Ramonda R, et al. Serum inflammatory biomarkers fail to identify early axial spondyloarthritis: results from the SpondyloArthritis Caught Early (SPACE) cohort. RMD Open. 2017;3(1):e000319.

14. Klingberg E, Strid H, Stahl A, Deminger A, Carlsten H, Ohman L, et al. A longitudinal study of fecal calprotectin and the development of inflammatory bowel disease in ankylosing spondylitis. Arthritis Res Ther. 2017;19(1):21.

15. Kopylov U, Starr M, Watts C, Dionne S, Girardin M, Seidman EG, et al. Detection of Crohn Disease in Patients with Spondyloarthropathy: The SpACE Capsule Study- A longitudinal study of fecal calprotectin and the development of inflammatory bowel disease in ankylosing spondylitis. J Rheumatol. 2018;45(4):498-505.

16. Ostgard RD, Deleuran BW, Dam MY, Hansen IT, Jurik AG, Glerup H. Faecal calprotectin detects subclinical bowel inflammation and may predict treatment response in spondyloarthritis. Scand J Rheumatol. 2018;47(1):48-55.

17. Olofsson T, Lindqvist E, Mogard E, Andreasson K, Marsal J, Geijer M, et al. Elevated faecal calprotectin is linked to worse disease status in axial spondyloarthritis: results from the SPARTAKUS cohort. Rheumatology (Oxford). 2019.

18. Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S47-58.

19. Striz I, Jaresova M, Lacha J, Sedlacek J, Vitko S. MRP 8/14 and procalcitonin serum levels in organ transplantations. Ann Transplant. 2001;6(2):6-9.

20. Stockley RA, Dale I, Hill SL, Fagerhol MK. Relationship of neutrophil cytoplasmic protein (L1) to acute and chronic lung disease. Scand J Clin Lab Invest. 1984;44(7):629-34.

21. Striz I, Trebichavsky I. Calprotectin - a pleiotropic molecule in acute and chronic inflammation. Physiol Res. 2004;53(3):245-53.

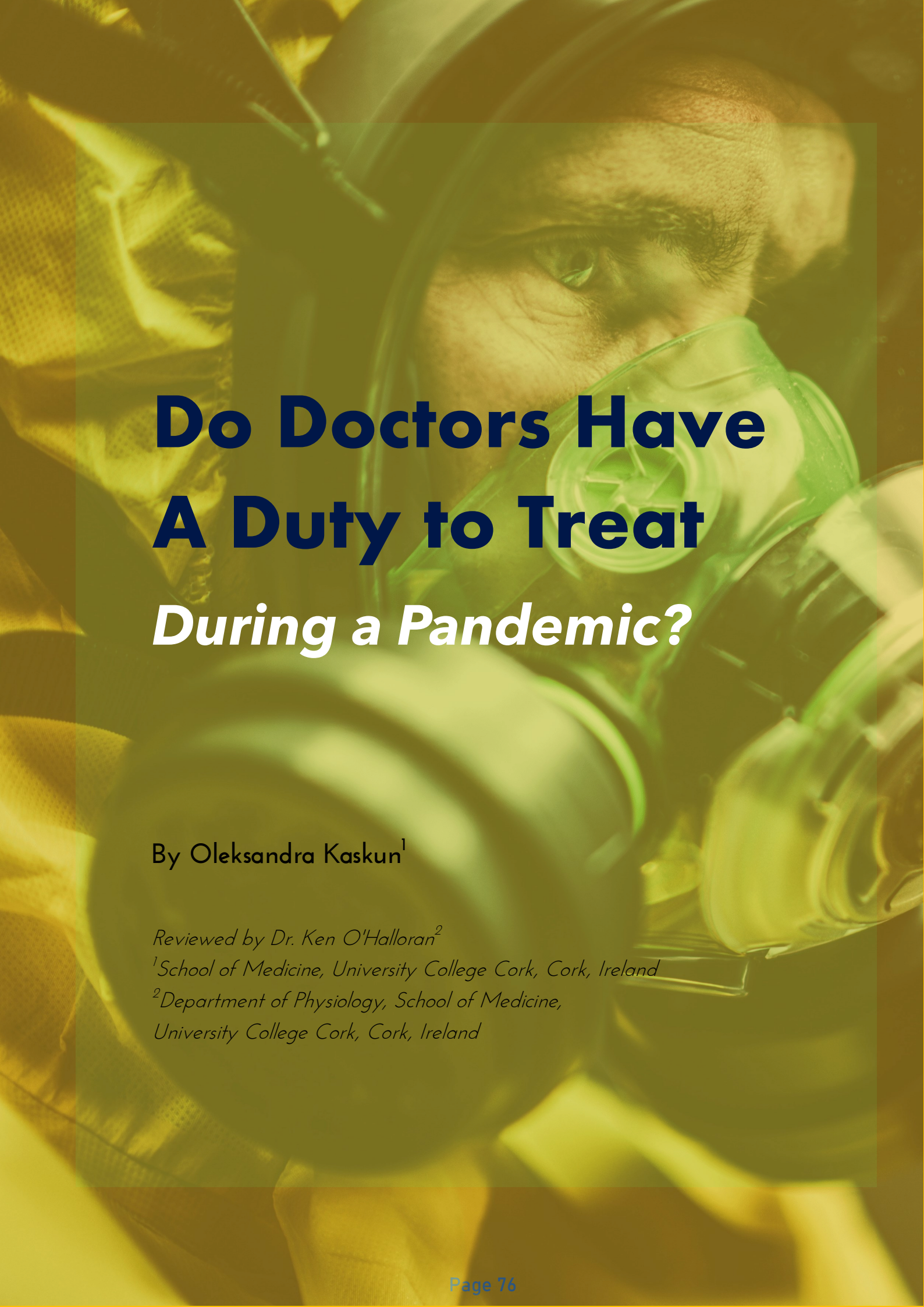
22. Gouveia EB, Elmann D, Morales MS. Ankylosing spondylitis and uveitis: overview. Rev Bras Reumatol. 2012;52(5):742-56.

23. Tibble JA, Sigthorsson G, Foster R, Scott D, Fagerhol MK, Roseth A, et al. High prevalence of NSAID enteropathy as shown by a simple faecal test. Gut. 1999;45(3):362-6.

24. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol. 2015;12(9):537-45.

25. Reveille JD, Arnett FC. Spondyloarthritis: update on pathogenesis and management. Am J Med. 2005;118(6):592-603.

26. Fernandez-Carballido C, Navarro-Compan V, Castillo-Gallego C, Castro-Villegas MC, Collantes-Estevez E, de Miguel E. Disease Activity As a Major Determinant of Quality of Life and Physical Function in Patients With Early Axial Spondyloarthritis. Arthritis Care Res (Hoboken). 2017;69(1):150-5.



Do Doctors Have A Duty to Treat *During a Pandemic?*

By Oleksandra Kaskun[1]

Reviewed by Dr. Ken O'Halloran[2]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]Department of Physiology, School of Medicine, University College Cork, Cork, Ireland

As a member of the medical profession:

I solemnly pledge to dedicate my life to the service of humanity;

These are the first two lines of The Physician's Pledge [1] – a contemporary revision of the Hippocratic Oath, sworn by physicians upon graduation.

Medicine is a humanitarian profession [2] and as stated in the Oath, doctors have a duty to help the sick. However, is this duty absolute? Can physicians refuse to treat patients? Even when there is significant risk to their own health? How about their duty as a spouse, parent or family member? These questions emerge during a health emergency and have been debated during the current COVID-19 pandemic.

During health emergencies throughout history, such as in times of plague or the more recent SARS epidemic of 2003 [2], many doctors realized the greater-than-normal personal risks (and even risk of death) associated with treating patients and decided to flee their practice. In doing so, they chose to protect their own health other than that of their patients and abandoned their colleagues, leaving them with a greater workload.

Was this a selfish decision? Almost half of the cases were among healthcare professionals during the SARS outbreak in Toronto [2]. The statistics for the total number of cases

are lower for COVID-19 – nearly 17% in Ontario [3] (as of May 2020) and 8% in Italy [4] (as of April), but it is still thousands of cases and the pandemic is not over yet. In addition to risking their own life, a physician risks infecting their family members, or leaving their spouses and/or children in case of death. Moreover, the chance of infection is increased with the shortage of Personal Protective Equipment (PPE) that many hospitals around the world have faced.

With these factors at play one can start to see the dilemma facing physicians.

The core ethical principle of beneficence describes the physician's duty of care to patients [5]. Relying heavily on this principle, the ethics manual of the American Medical Association asserts that "physicians have an obligation to provide urgent medical care during disasters […] even in the face of greater than usual risks to physicians' own safety, health, or life" [6]. Canada's Code of Ethics does not go as far [7], but there is a notion of physicians implicitly accepting inherent risk upon joining the profession [8]. However, a sick doctor cannot be of much assistance to current patients, and if the physician does not survive the infection, then they will not be of assistance to future patients either, thereby not fulfilling their duty.

The physician's ethical duty to self-care is mentioned in The Physician's Pledge with the following words "I will attend to my own health, [and] well-being" [1]. The duty to self-care was reiterated by the Medical Council in Ireland when commenting on the coronavirus outbreak [9]. Furthermore, the British Medical Association reassures their doctors that "there are limits to the risks [physicians] can be expected to expose [themselves] to" and that doctors "can refuse to treat patients if [their] PPE is inadequate, [or they] are at high risk of infection" [10]. It is interesting to consider that North America, Ireland and the UK place a different emphasis on a physician's duty, serving to increase the ethical uncertainty faced by physicians around the world regarding their duties during a pandemic.

To further complicate this discussion on duty to care for patients versus the duty to self-care, let us consider the additional factor of overworked physicians. Medical resources and services have been strained during COVID-19,with the number of ICUs at or near capacity [11]. With this large inflow of patients and the risk for infection, physicians have been required to work longer hours and have been under additional stress. This situation impacts a physician's duty to self-care, and the strain on their body makes them more vulnerable to infection due to a

lowered immune system. Once infected, they are at increased risk of spreading the infection to vulnerable patients, thereby going against the ethical principle of non-maleficence – which states that a physician must not incur additional harm to a patient [5].

Moreover, even in non-pandemic times, studies show that physicians who experience burnout are more likely to perform medical errors [12]. The stress, workload and burnout experienced by physicians can be amplified in a pandemic and can prove counterproductive to the duty of care to patients that physicians are trying to uphold, if patients are subjected to greater risk of medical error.

So, do doctors have an ethical duty to treat during a pandemic? The answer remains unclear. Some countries and their medical associations support the idealistic humanitarian viewpoint of medicine and the physician's duty to care for patients. Others are cautioning that a physician also has a duty to care for themselves and their own health. How can a balance be stricken between both duties safely, in a pandemic where protective resources are not guaranteed, without creating heroes and villains?

In this dilemma, we see a juggling of ethical principles as well as each physician's personal values to be able to make a decision of whether or not to go to work during COVID-19, or any other public health emergency, including more lethal ones. As a suggestion, legislation should not force physicians to tend to their duty to care for patients when risk is much higher than normal, while their jobs are held securely. However, this also poses the complication of defining "much higher than normal" risk, as well as whether physicians who do not attend get compensated?

An option is to have medical professionals volunteer their services in a public health emergency when sufficient protective measures are in place. Moreover, if internationally qualified doctors or final year medical students are permitted to volunteer, it can help reduce the strain on existing medical professionals and facilitate the response in medical emergencies. This also comes with some complications however, such as PPE shortages, potential variance in quality of care for patients, and a strain on the existing personnel to orient and train the incoming volunteers.

There is, unfortunately, no clear answer to whether doctors have a duty to treat during a pandemic and when proposing potential solutions, one encounters further ethical dilemmas. Nonetheless, one thing is certain - the COVID-19 pandemic will reshape our society and our healthcare systems, and I hope that if another medical emergency were to arise, we would be better prepared to handle it.

References

1. World Medical Association. The Physician's Pledge. World Health Association Declaration of Geneva, v2017
2. Jauhar S. In a Pandemic, Do Doctors Still Have a Duty to Treat? The New York Times, April 2:2020
3. Pelley L. Nurses, lab workers, physicians among 'alarming' number of health-care workers with COVID-19. CBC News, May 15:2020
4. Reguly E. Italian doctors' fatalities reach tragic levels as they fight COVID-19 in overburdened hospitals. The Globe and Mail, April 3:2020
5. Simonds AK, Sokol DK. Lives on the line? Ethics and practicalities of duty of care in pandemics and disasters. European Respiratory Journal 2009;34:303-309.
6. American Medical Association. Physicians' Responsibilities in Disaster Response and Preparedness. Code of Medical Ethics Opinion 8.3, 2020
7. Canadian Medical Association. CMA code of ethics (update 2004): Article 18. Ottawa: Canadian Medical Association, 2004
8. Davies CE, Zlotnik Shaul R. Physicians' legal duty of care and legal right to refuse to work during a pandemic. Canadian Medical Association Journal 2010;182(2):167-170.
9. Cullen P. Coronavirus: Doctors have 'ethical duty' to self-care. The Irish Times, March 9: 2020
10. British Medical Association. COVID-19: refusing to treat where PPE is inadequate. British Medical Association, June 11:2020
11. Salter J, Tanner L. 'Irresponsible' to rely on hospital capacity data amid U.S. coronavirus resurgence: experts. Global News, June 27: 2020
12. Tawfik DS, Profit J, Morgenthaler TI, et al. Physician Burnout, Well-being, and Work Unit Safety Grades in Relationship to Reported Medical Errors. Mayo Clinic Proceedings 2018;93(11):P1571-1580.

Attitudes Towards the use of Mechanical Restraints in Psychiatric Facilities:

Contrasting Practices In Ireland and Ontario

By Leah Komer[1]

Reviewed by Dr. Ken O'Halloran[2]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]Department of Physiology, School of Medicine, University College Cork, Cork, Ireland

Ethical Discussion

The use of restraints on patients with mental illness is controversial within healthcare and society at large.

One must balance the liberty and safety interests of patients and staff to minimise harm and maximize freedom. The inhumanity of inappropriate restraint use in hospitals has been portrayed in the media and popular culture. Restraints must only be used with proper legal authorization. Ethical issues related to the use of restraints arise when considering patient autonomy, power imbalances between patients and staff, gender differences, and the safety of all persons involved. The term "restraint" is broad and its meaning can vary across different settings. For example, in the province of Ontario, in Canada, restraint is defined under the Mental Health Act 1990 as to

"place under control when necessary to prevent serious bodily harm to the patient or to another person by the minimal use of such force, mechanical means or chemicals as is reasonable having regard to the physical and mental condition of the patient." [1]

In psychiatry, a restraint can be categorized as environmental, chemical, or physical. Environmental restraint involves limiting the patient's access to their surroundings by keeping them in seclusion rooms or locked units. Chemical restraint involves the use of psychotropic medications to place a person under control to manage harmful behaviours and prevent their occurrence. Lastly, physical restraints or mechanical restraints involve limiting the patient's bodily movement by means of healthcare staff or security holding him or her down or using devices such as lap belts, wrist restraints, pelvic restraints, or sheets. Restraint is not a form of treatment to which a patient consents and should only be used when less intrusive measures to control behaviour have been considered. Least restrictive measures should be considered first, since all forms of restraint can be traumatizing for the patient [2].

Having reviewed the literature and completed psychiatry placements both in Ireland and Ontario, I have learned that these settings have different attitudes towards the use of mechanical restraints. While both agree that least restrictive measures need to be considered first, there appears to be more reluctance towards using mechanical restraint devices in Ireland than in Ontario. Conversely, this does not imply that in Ontario mechanical restraints are preferred, simply that this approach is more commonly used. Between 2006 and 2010, approximately one quarter of psychiatric inpatients in Ontario were restrained, and of that, 20.7% were restrained by mechanical or physical means [2].

During my psychiatry placement in Ontario, there were few instances when I witnessed a patient being restrained. In these circumstances, after failed attempts to control an aggressive situation with verbal talking-down techniques and oral PRN (as needed) medication, the patients were placed in seclusion. They were subsequently monitored via a room camera and staff attending periodically to check on their wellbeing. The only time I saw a patient in mechanical restraints was when they were being moved from the maximally secure facility to the minimally secure unit for treatment. No form of restraint is consistently more traumatizing for a patient than another, and by no means should it ever be used as part of the patient's treatment. Additionally, there are risks and negative outcomes related to each form of restraint. However, understanding the risks, evaluating the current situation, and having the option to use different modalities of restraint can be beneficial for both patients and staff. For example, it may not be safe to use chemical restraint in certain patients based on their medical and drug history, as it can lower seizure threshold, precipitate respiratory depression or cardiac arrest, or result in neuroleptic

malignant syndrome [2]. In these patients, environmental or mechanical restraint would be a safer option; however, these are not without consequences either. Environmental restraint can lead to a patient feeling isolated, stigmatized or hopeless, and can increase suicidal ideation and self-harm [2]. Physical restraints also carry some of these risks in addition to thrombosis, blunt trauma, and even death [2]. Patients who are restrained need to be carefully monitored to mitigate some of these risks [3]. While mechanical restraint is used under specific circumstances in Ontario, this is not default practice for challenging behaviours, and other techniques are considered first.

In Ireland, only one psychiatric facility, the Central Mental Hospital in Dublin, is approved to use mechanical restraints [4]. In 2016, this facility reported using mechanical restraints on less than five occasions [4]. Under legislation of the Irish Mental Health Act 2001, "a person shall not place a patient in seclusion or apply mechanical means of bodily restraint to the patient unless such seclusion or restraint is determined, in accordance with the rules made under subsection (2), to be necessary for the purposes of treatment or to prevent the patient from injuring himself or herself or others and unless the seclusion or restraint complies with such rules."[5] The Mental Health Commission implemented rules in accordance with this section which states, "a person may not be placed in bodily restraint or seclusion unless it is absolutely necessary or as a last resort."[6] In 2016 there were 52 approved centres in Ireland for the use of physical restraint, which involves using physical force, not devices, to restrict movement [7]. Abandoning the use of mechanical restraints certainly has commendable benefits such as increasing patient autonomy, moving away from previously cruel practices, and preventing injury to patients and staff. From my experience with psychiatry in Ireland, the thought of using mechanical restraints on psychiatric patients was met with disdain by mental health professionals and was perceived as reverting to inhumane practices. While there is no denying that psychiatry has a dark history of treating mental illness, and current practices can still be improved, the appropriate use of mechanical restraints theoretically should not pose more risk than any other form of restraint. However, the justification to remove the use of mechanical restraint from practice in Ireland holds merit and allows for comparisons in practice to be made.

The use of restraints in patients with mental illness is controversial. However, considering risks and benefits to patients and staff from all forms of restraint allows healthcare providers to challenge current practices and beliefs and lead to improvements in care. The traumatic effects of restraint on patients cannot be ignored. Sensitivity and respect always need to be maintained when they are used. Having observed practices in both Ireland and Ontario, I conclude that there are valid points to be made on both sides of this ethical debate. Perhaps developing less harmful techniques to manage challenging behaviours can make psychiatric facilities and hospitals as safe as possible for patients and staff, and efforts should be made to strive towards this.

References

1. Mental Health Act, R.S.O. 1990, c. M.7 [Internet]. [cited 2020 Jun 2]. Available from: https://www.ontario.ca/laws/statute/90m07/v5

2. Emanuel LL, Taylor L, Hain A, Combes JR, Hatlie MJ, Karsh B, et al. Module 13d: Mental Health Care: Seclusion and Restraint: When All Else Fails [Internet]. [cited 2020 Jun 2]. Available from: www.patientsafetyinstitute.ca

3. Sethi F, Parkes J, Baskind E, Paterson B, O'Brien A. Restraint in mental health settings: Is it time to declare a position. Br J Psychiatry. 2018 Mar 1;212(3):137–41.

4. Restrictive Practices: Use of Seclusion and Restraint Activity Report 2016. Mental Health Commission [Internet]. Available from: https://www.mhcirl.ie/File/restrict_prac2016.pdf

5. Mental Health Act, 2001, Section 69 [Internet]. [cited 2020 Jun 2]. Available from: http://www.irishstatutebook.ie/eli/2001/act/25/section/69/enacted/en/html#sec69

6. Reidy M. Rights and wrongs of patient restraint. WIN. 2008;16(2):22-23. Available from: https://www.inmo.ie/tempDocs/legal_Feb08.pdf

7. Mental Health Commission (2009), Code of Practice on the Use of Physical Restraint in Approved Centres. Version 2. (Dublin). Available from: https://www.mhcirl.ie/File/Revised_COP_PR.pdf

A COVID Question

The Impact on Our Nursing Home Residents

By Aoife McDonagh[1]

Reviewed by Dr. Colin Bradley[2]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of General Practice, School of Medicine, University College Cork, Ireland

Introduction

COVID-19, a novel coronavirus which targets the respiratory system, has had a significant impact on Irish nursing homes.
The virus was declared a global pandemic in March 2020, and as of 14th June the Health Protection Surveillance Centre has reported 258 clusters of cases in nursing homes, comprising 21% of all cases in Ireland and associated with 943 deaths [1]. This pandemic is a source of many ethical dilemmas — an example being the ethical issues arising from enforced social isolation imposed on residents during lockdown.
The cocooning of residents in nursing homes raises a question with no simple answer — does the risk this isolation poses to the wellbeing of elderly residents outweigh the benefits of such strict measures to protect them from COVID-19?
The adverse effects of isolation, although relevant in any infectious outbreak, are compounded in this instance by the unprecedented scale of the coronavirus pandemic and the immense pressure on the healthcare system as it faces this new threat to health.
Even in the chaos of a global pandemic, the ethical principles at the root of all healthcare decisions, namely non-maleficence, beneficence, autonomy, and justice remain pertinent.

Nonmaleficence

A phrase attributed to the physician Hippocrates, 'primum non nocere', or 'first, do no harm', encapsulates the principle of nonmaleficence. It pertains to an ethical and legal obligation to avoid harm, balancing benefits of treatment against potential pain and suffering [2].
COVID-19 poses a significant threat to the elderly. People over 60 years of age are considered high risk; those over 70 fall into the very high-risk category [3].
These age groups are predominant in residential care facilities, where the risk of infection is higher due to people living in close proximity and the movement of carers between residents [4]. Guidelines exist to prevent the virus entering facilities, as an outbreak can have a catastrophic impact on a nursing home with vulnerable residents. However, it is difficult to remain case-free [5].
Guidelines already in place for influenza outbreaks highlight the importance of vaccination and antivirals; these are not applicable to COVID-19. Therefore, significant emphasis is placed on isolation in coronavirus-specific guidelines. Exclusion of symptomatic visitors in the case of influenza is less restrictive than the strict ban on all visitors, symptomatic or not, during the current pandemic [6].
Confirmed cases are confined to their room, and visiting restrictions apply to everyone, regardless of test result.
Research shows that loneliness and social isolation in the elderly have been linked to physical as well as mental conditions, including anxiety, depression, hypertension, and a weakened immune system [7]. This isolation is necessary to protect the vulnerable from the virus, but it harms them socially. Those with dementia, a common condition in long-term care facilities, may experience a significant deterioration in their condition during lockdown [8]. Emotional needs of all residents as well as signs of physical deconditioning such as reduced mobility, confusion, new swallowing problems and constipation should be monitored according to guidelines [5].
The harm that may result from isolation measures conflicts with the aim of non-maleficence.

Beneficence

Healthcare decisions must be made in the best interest of the patient [9]. Guidelines urge healthcare professionals to keep residents isolated to protect them from infection, but this is at the expense of their mental wellbeing. A balance must be achieved when deciding what is best for each individual patient, taking into account the mental health effects of isolation.
In order to truly uphold the wellbeing of the patient, all needs should be met: mental and social as well as physical, as is suggested by the biopsychosocial model of health [10]. Anxiety

may be felt by residents who are at risk of contracting COVID-19, causing their sleeping patterns and mental health to suffer [11]. Confirmed cases may fall victim to loneliness when quarantined to a room for the safety of others, adversely impacting their psychological and social wellbeing. It is difficult to fully satisfy the principle of beneficence during this pandemic; physical health benefits of isolation are maximised, but mental wellness is infringed upon by doing so, illustrating how intricately linked the principles of beneficence and non-maleficence are. In recent times, the occasional visit through a window from family members can raise spirits. However, this is no replacement for the comfort that comes with physical contact.

Autonomy

For those dependent on carers, maintaining as much independence as possible is paramount for good quality of life [12]. Informed consent can be challenging in cases of dementia. The use of Personal Protective Equipment may be distressing to those with dementia; they may not understand why it is being worn, and it is more difficult to read facial expressions with regard to communication [13]. When being tested for the coronavirus, residents with dementia may not fully understand what is happening, and this can be frightening. It cannot be assumed that there is no capacity, but someone's capacity for decision-making can be subject to change. All patients have the right to refuse a test [14]. Autonomy must be acknowledged here, with dignity and respect upheld [15].

Long-term care facilities are among the institutions which locked down earliest during this crisis, and so this specific population has been isolated for longer than most. Restricting movement and being confined to one room represents a loss of autonomy for elderly residents who depend on social interaction to break up their day [16]. A cohort who are dependent on others for help in a time when understaffing is being exacerbated by the increased pressure on healthcare workers, the restrictions imposed on nursing home residents are especially severe. With restricted contact from family and friends, there is the risk of dying alone in a facility, something that most would not choose. Residents with the virus have no choice but to forgo social interaction for their own safety and the safety of others in the facility. A phone call is not always possible with the staff under pressure and some residents being unable to make a call themselves. This lack of choice, although necessary to protect residents from harm, signifies a loss of control which can predispose to anxiety and depression.

Justice

With such demand on the healthcare system, the pressure to prioritise resources has sparked debate among professors in the fields of bioethics and philosophy [17]. Some countries, for example Italy, opted for the utilitarian approach, prioritising those with a higher chance of therapeutic success and hence achieving the greatest benefit for the greatest number of people [18]. It is not ethically justified, though, to make a decision based solely on age [19]. As older persons have an equal right to health and life as everyone else, such decisions should be made on the basis of medical needs, not simply age.

Although much has been done by compassionate volunteers to support the elderly during lockdown, a type of ageism has emerged in the midst of this pandemic which represents a lack of solidarity with the elderly population; this prejudice can leave nursing home residents feeling even more isolated, further impacting their psychological wellbeing and health outcomes [19, 20].

Conclusion

A compelling question is brought to light here; even if free from the virus in a facility with confirmed cases, is it possible to truly achieve health? The simplest definition of health equates with the absence of disease, but an individual's mental and social wellbeing should also be emphasised, as implied by other definitions [21].

When caring for nursing home residents during this pandemic, it can be hard to follow one

principle without breaching another; for example, when exacting beneficence and isolating residents to protect their physical health, this causes mental health to suffer, at odds with the principle of non-maleficence. The social and psychological wellbeing of many residents is compromised in a bid to protect them from this virus.

As in the prioritisation of resources, there seems to be the inevitable prioritisation of one ethical principle over another, resulting in a balancing act to try to do right by the individual patient and their family. Discussion among healthcare professionals at a population level, and with regards to individual cases, is one way of taking a step towards resolution of these ethical dilemmas.

References

1. Nursing Homes - Summary paper provided to Special Committee on COVID-19 Response. Department of Health; 2020 p. 4.
2. Morrison E. Ethics in Health Administration: A Practical Approach for Decision Makers [Internet]. 3rd ed. Sudbury, Massachusetts: Jones and Bartlett Publishers; 2006 [cited 5 June 2020]. Available from: https://erl.ucc.edu.gh/jspui/bitstream/123456789/3010/1/%5BEileen_E._Morrison%5D_Ethics_in_Health_Administrati%28BookZZ.org%29.pdf
3. People at higher risk from coronavirus [Internet]. Www2.hse.ie. 2020 [cited 5 June 2020]. Available from: https://www2.hse.ie/conditions/coronavirus/people-at-higher-risk.html
4. Allan S. Care homes and the spread of COVID-19 | PSSRU [Internet]. Pssru.ac.uk. 2020 [cited 26 July 2020]. Available from: https://www.pssru.ac.uk/blog/care-homes-and-the-spread-of-covid-19/
5. BGS. Managing the Covid-19 pandemic in care homes. Dev Biol (Basel). 2020;132(March):425–7.
6. HSE. Public Health Guidelines on the Prevention and Management of Influenza Outbreaks in Residential Care Facilities in Ireland 2019/2020. Dublin: HPSC; 2020 p. 7, 27.
7. Social isolation, loneliness in older people pose health risks [Internet]. National Institute on Aging. 2019 [cited 5 June 2020]. Available from: https://www.nia.nih.gov/news/social-isolation-loneliness-older-people-pose-health risks#:~:text=Health%20effects%20of%20social%20isolation,Alzheimer's%20disease%2C%20and%20even%20death.
8. Alzheimer Europe recommendations on promoting the wellbeing of people with dementia and carers during the COVID-19 pandemic [Internet]. Alzheimer-europe.org. 2020 [cited 14 August 2020]. Available from: https://www.alzheimer-europe.org/Policy/Our-opinion-on/Wellbeing-of-people-with-dementia-during-COVID-19-pandemic
9. Kinsinger F. Beneficence and the professional's moral imperative. Journal of Chiropractic Humanities. 2009;16(1):44-46.
10. A look at Covid-19 through a biopsychosocial lens — The Good Physio [Internet]. The Good Physio. 2020 [cited 26 July 2020]. Available from: https://www.thegoodphysio.co.uk/blog/a-look-at-covid-19-through-a-biopsychosocial-lens
11. Department of Health. Ethical considerations relating to long-term residential care facilities. Dublin: Government of Ireland, gov.ie; 2020 p. 1, 2.
12. Smebye K, Kirkevold M, Engedal K. Ethical dilemmas concerning autonomy when persons with dementia wish to live at home: a qualitative, hermeneutic study. BMC Health Services Research [Internet]. 2015 [cited 14 August 2020];16(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717656/
13. Health Service Executive. COVID-19 TESTING AND THE PERSON LIVING WITH DEMENTIA. HSE; 2020 p. 1.
14. McGrath D. Consent is crucial for coronavirus testing. But in nursing homes, it isn't always so simple [Internet]. TheJournal.ie. 2020 [cited 15 August 2020]. Available from: https://www.thejournal.ie/nursing-homes-consent-coronavirus-testing-hse-5093590-May2020/
15. Courtin E, Knapp M. Social isolation, loneliness and health in old age: a scoping review. Health & Social Care in the Community. 2015;25(3):799-812.
16. Parker J, Mirzaali M. The Moral Cost of Coronavirus | Journal of Medical Ethics blog [Internet]. Journal of Medical Ethics blog. 2020 [cited 5 June 2020]. Available from: https://blogs.bmj.com/medical-ethics/2020/03/16/the-moral-cost-of-coronavirus/
17. Archard D, Caplan A. Is it wrong to prioritise younger patients with covid-19?. BMJ [Internet]. 2020 [cited 15 August 2020];369(8242):m1509. Available from: https://www.bmj.com/content/369/bmj.m1509
18. Martínez-Sellés D, Martínez-Sellés H, Martinez-Sellés M. Ethical Issues in Decision-making Regarding the Elderly Affected by Coronavirus Disease 2019: An Expert Opinion [Internet]. Ecrjournal.com. 2020 [cited 5 June 2020]. Available from: https://www.ecrjournal.com/articles/Ethical-Issues-Elderly-Affected-By-Coronavirus-2019
19. Kornfeld-Matte R. Leaders speak out about their concerns regarding older people in the context of COVID-19 [Internet]. Who.int. 2020 [cited 26 July 2020]. Available from: https://www.who.int/news-room/feature-stories/detail/leaders-speak-out-older-people-covid-19
20. Fraser S, Lagacé M, Bongué B, Ndeye N, Guyot J, Bechard L, et al. Ageism and COVID-19: What does our society's response say about us? Age Ageing. 2020;1–4.
21. Sartorius N. The Meanings of Health and its Promotion. Croatian Medical Journal. 2006;47(4):662–664.

[This page has been intentionally left blank. Please turn over.]

Gothenburg Exchange

By Alison O'Shea[1]

Reviewed by Dr. Elaine Walsh[2]
[1]School of Medicine, University College Cork, Cork, Ireland
[2]Department of General Practice, School of Medicine, University College Cork, Cork, Ireland

Background on Gothenburg

Gothenburg, being Sweden's second largest city, and bearing many similarities to Cork, has earned itself the nickname of "The People's Republic Of Sweden". As part of clinical our clinical rotations in 4th year, myself and ten other students were lucky enough to be chosen to participate in an exchange programme with the University of Gothenburg, and have the opportunity to live and study there for a month. Sweden's healthcare system is renowned worldwide, and it was a wonderful opportunity to work alongside medical professionals operating in a different system and cultural setting to the one we see here at home. There are a number of differences between Ireland's healthcare system and that seen in Sweden. A key difference is the emphasis placed on private healthcare: While private care is an element of Sweden's healthcare system, services are predominantly funded by the taxpayer, and while the quality of healthcare in Sweden is universally well-regarded, waiting times for GP visits, specialist appointments and operations are seen to be one of the key issues facing the medical system there.

First Impressions

On our arrival in Gothenburg, we were warmly welcomed by the medical teams and professionals, allowing us to integrate seamlessly into the new environment. The majority of the staff and students were able to speak English fluently, so lectures and tutorials were extremely well run and provided us with an excellent setting in which to learn.
The medical teams are structured quite differently in comparison to those in Ireland. There seemed to be no hierarchy as such, everybody wore the same scrubs, and even the consultants asked us to address them by their first name. This allowed us to integrate and interact with the team with ease, and really allowed us to feel included and valued.

The 11 Cork-based students were divided into the specialties which we had requested when applying for the programme. I, along with one other student was attached to the obstetrics and gynaecology team for a month, while three students were attached to each of the medicine, paediatrics and and surgical teams. The OBGYN experience we had was second to none. The team allowed us to get very involved clinically, and as a result we performed speculum exams, observed vaginal deliveries, and also scrubbed in on a number of C-Sections. When dealing with patients the language barrier was a bit more problematic, however the team were always more than willing to translate histories for us.

Fertility Medicine in Sweden

In Sweden, fertility medicine is offered to couples struggling to conceive naturally through the public system and we spent one week in the fertility department where we observed IVF egg extractions and implantations and we also sat in on couples' consultations. According to national figures, approximately 12,000 IVF treatments are given annually in Sweden, double that of Ireland. Literature on the topic points to ever increasing government funding for IVF and fertility treatment in Sweden, thereby allowing fertility care to become more affordable and accessible as a result [1]. Here in Ireland, Assisted Human Reproduction treatment is not currently funded by the Irish Public Health Service, couples oftentimes have to pay upwards of €4500 for one course of IVF treatment [2]. Cost means that IVF in Ireland is quite an exclusive option, with many couples finding the financial burden prohibitive. Having the chance to see the benefits and rewards of such a system was truly eye-opening and is something I'll treasure for the rest of my career. We also spent a few days in an abortion clinic, which again was incredibly educational, and a new learning experience for us as medical students.

Fika

During our down time, if you could even call it that, we made the most of every minute. Most days after placement we would head into Gothenburg city and meet up for fika, the most important part of any Swede's day. Fika is a Swedish tradition where one meets up with friends, usually mid-afternoon, for a sweet treat and a catch up. The public transport system connecting the city to the surrounding suburbs is excellent, and furthermore we all stayed together in an accommodation building approximately 15 minutes from the city centre by tram, which arrived every 3-5 minutes, certainly different to what we're used to in Ireland! We tried to be as adventurous as we could with the local cuisine which for the most part was delicious, particularly the local seafood and fresh baked goods. I'm a pescatarian so the Nordic cuisine suited me down to the ground. Our student buddies who we were partnered up with by the academy were wonderful. They brought us ice skating, rock climbing and showed us all the best pubs and restaurants. The group were so enthusiastic and accommodating. It really added to our whole trip. We're still in contact with many of them, some hoping to visit us in Ireland in the post-covid era. A group of us took a boat trip and explored the Archipelago coastline on our final weekend and went trekking to various look out points, a highlight for many of us. At the weekends we travelled to both Oslo and Stockholm by train and explored these two beautiful cities, we were so lucky that both capital cities were in such close proximity to Gothenburg.

Recommendation to other Students

Partaking in this exchange programme has undoubtedly been my most cherished memory from university so far, I would highly recommend everyone to apply for if given the opportunity. The experience I had both medically and culturally will most definitely stand to me for the rest of my career.

References

1. "Fertility Treatment." HSE.ie, www2.hse.ie/conditions/child-health/fertility-problems-and-treatments/fertility-treatment.html.

2. "Employment, Social Affairs & Inclusion." Sweden - Employment, Social Affairs & Inclusion - European Commission, ec.europa.eu/social/main.jsp?catId=1130.

Risk Assessment of Non-Communicable Diseases (NCDs) in Rural Maharashtra, India

By Shivika Marwaha[1]

Reviewed by Dr. Colin Bradley[2]

[1]School of Medicine, University College Cork, Cork, Ireland

[2]Department of General Practice, School of Medicine, University College Cork, Ireland

Introduction

Last summer I got the chance to conduct risk assessment surveys in rural India as well as physiological tests to measure blood pressure (mmHg) and Random Blood Sugar (mg/dL) for a research paper I was writing in High School which is being continued in my first year of Medical School. The research question I addressed was - **"To what extent do socioeconomic factors influence the risk of developing lifestyle diseases such as Obesity, Hypertension and Type II Diabetes Mellitus in Rural and Urban Indian women aged 35-55 years?"** Alongside a nurse and doctor from a non-profit organization in India called the Family Planning Association of India, we gathered data from 50 rural women residing in the Kolvan Valley in Maharashtra. Having lived in the urban parts of India for the majority of my life, this opportunity exposed me to healthcare in rural India and language barriers due to the diversity of subindian cultures.

Key takeaways

The process of gathering qualitative and quantitative data from a rural population was a very enriching learning experience. One of the most important things I learnt was the unfortunate disparity that still exists in rural and urban India. A lack of resources and hygiene in public hospitals means that healthcare in rural areas is not a priority for those residing in the rural parts of India. Even the closest hospital for this village was 60km away. Moreover, although equipment and medicines were available, accessibility, in terms of distance and transportation seemed to be a major issue. We also noticed an association between food security and socioeconomic factors. For instance, a majority of the women were told to drop out of school after the 8th grade, get married and look after their family. They would cook food and distribute it to their family members and eat whatever was left in the pot, which is often the food with the least nourishment.

Some women even consumed smokeless tobacco because it acted as a meal substitute to fulfil their hunger. After speaking to the women, we understood that there was a common understanding amongst them that lower education levels are often associated with a lower status in their society which in turn affected their food intake and nourishment at home.

Challenges faced

As the coordinator of this project, I was leading a group of students from an international school. A challenge we came across was that neither of us spoke the local dialect of Marathi. This hindered the rapport building process which is essential in establishing a healthy doctor-patient relationship. We overcame this by employing gestures and displaying empathy by holding a lady's hand if she seemed worried or confused.

Moreover, we were expecting a larger group of women to show up to this free of cost health screening considering the population of the village. However, several of the women claimed that they did not see the objective of the check-up as they had not been experiencing any symptoms indicative of physical disease; however, this is a key aspect of a lifestyle disease. Non communicable diseases or lifestyle diseases are a result of the lifestyle habits employed throughout one's life and are often asymptomatic. They are very much preventable but having spoken to the women, we realised that most of the rural women sample did not see the need to go to the nearest public hospital without seeing any visible symptoms such as fever, hot flushes, bleeding, redness, etc.

Conclusion

Risk assessment in rural Maharashtra was an eye opening experience for me. Seeing a lack of doctors and resources in public hospitals, worrisome Body-Mass Indices, blood pressure and blood sugar readings first hand left me in awe. Malnutrition, whether it be anorexia or obesity, low or high blood sugar, is a major issue in all Low-Middle Income Countries, including India considering the vast difference in the development rate between its rural and urban parts. Some have access to more than required while others are struggling to access the bare minimum.

This research has also been incorporated in a project I am working on with Dr John O'Donoghue and Dr Patrick Henn at the ASSERT Center in University College Cork. Alongside other projects, we intend to do a comparative study with low and high income countries such as Malawi and Ireland respectively to see the applicability of the above mentioned risk factors in developing countries.


CITISCAN - Radiology
2018CS0012503-1
87 %

UCC

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh