pISSN: 2220-7562
eISSN: 2617-9482
CODEN: JBUMB7
Recognized by HEC & PMDC

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 13 Issue 4, October - December 2023

Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA, DHA Phase II, Karachi

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC & PMDC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
ICMJE at https://www.icmje.org/journals-following-the-icmje-recommendations/#J
Bahira University DSpace Repository at http://111.68.99.22:8080/xmlui/handle/123456789/6388,
Pakistan Scientific and Technological Information Center (PASTIC) at http://pastic.gov.pk/

Correspondence Address:
Editor, JBUMDC, Bahria University Medical & Dental College, Adjacent PNS SHIFA,
DHA Phase II, Karachi Pakistan
+92-21-35319491-9
https//jbumdc.bahria.edu.pk
editor.bumdc@bahria.edu.pk
https://www.facebook.com/jbumdc/, https://www.facebook.com/journal.bumdc.7
Published by: Bahria University Health Sciences, Campus Karachi

JBUMDC

Journal of Bahria University Medical & Dental College

Recognized by HEC & PMDC

JBUMDC Journal of Bahria University Medical & Dental College
Volume-13, Issue-4. October-December 2023

CONTENTS

Editorial **Open Access**

Academic Misconduct: A Major Challenge to the Medical Profession

Sannia Perwaiz Iqbal

How to cite this Article:
Iqbal SP, Academic Misconduct: A Major Challenge to the Medical Profession. J Bahria Uni Med Dental Coll. 2023;13(4):248-9 DOI: https://doi.org/10.51985/JBUMDC2023262

Integrity is a fundamental quality expected from all individuals involved in academia, including students, faculty, and healthcare professionals. However, there has been a significant increase in complaints regarding academic misconduct among medical students in recent years. The erosion of moral values and ethics observed in society appears to have contributed to the pervasive academic misconduct that is infiltrating our medical educational system.

Academic misconduct refers to actions that provide an unfair advantage or disadvantage to oneself or others within the academic community.[1] Examples of academic misconduct include plagiarism, cheating, completing academic work for other students, obtaining information from previous exam takers, copying answers from nearby classmates, having someone else mark attendance on behalf of a friend, and forging a teacher's signature. These actions undermine the integrity of medical education and have serious consequences. The prevalence of cheating among medical students worldwide varies widely, ranging from 0% to 58%.[2] In Pakistan, studies estimate that approximately 50 to 80 percent of medical students are involved in some form of academic misconduct.[3] Another study from Pakistan found that around 65% of medical students considered academic misconduct to be acceptable, and 34% admitted to participating in some form of misconduct.[4] A recent report revealed that 44% of students confessed to fabricating clinical histories, while 28% admitted to writing false examination findings without actually conducting the examinations.[5] A more recent study showed that students were aware of what constituted academic misconduct, but this awareness did not deter them from engaging in such practices.[6] In India, 20% of students saw no issue with academic misconduct, and over 33% intended to continue these practices in the future.[7] In contrast, in the UK, only 2% of medical students confessed to copying during degree examinations, with 98% considering it to be wrong.[8] Similarly, in a study conducted in the USA, only 4.7% of students admitted to cheating.[9] Similar to any other profession, the medical field is not without the individuals who engage in unethical practices. There is substantial evidence indicating a high prevalence of academic dishonesty among faculty members as well.[10] Instances of faculty members exhibiting favouritism towards individuals with influential connections, purposefully failing students due to personal grudges, accepting bribes in exchange for passing students, manipulating attendance records to ensure that no student falls short on attendance in clinics and medical rounds, inflating internal assessment marks to guarantee a minimum passing score, turning a blind eye to cheating happening right in front of them, and even actively encouraging cheating by colluding with assistants to provide students with exam-related materials. These are some of the forms of academic misconduct perpetrated by faculty members. Within the realm of research, unethical practices such as plagiarism, data falsification, paying for authorship in research papers, ghost and gift authorship are frequently reported. The extent of this problem is quite challenging to ascertain, but it is evident that various forms of academic misconduct exist across different settings. These actions undermine the integrity of medical education and carry significant implications.[10] Various studies indicate that such practices have become more prevalent as faculty members face increasing pressure to maintain their research endeavours. Faculty members encounter substantial demands to uphold high standards of clinical practice, educate and train future medical professionals and researchers, conduct scientific investigations, and secure funding for both clinical and research pursuits.[11] At the same time they are also expected to adhere to various financial and regulatory requirements. Within this highly competitive academic landscape, the heightened expectations and demands may inadvertently or intentionally lead to instances where faculty members engage in academic misconduct. The prevalence of unethical behaviour among academicians is on the rise, and there appears to be a lack of willingness among faculty to do away with these practices. Those who hold firm conviction to adhere to ethical practice often find themselves in subordinate positions within the hierarchical structure, which makes it challenging for their voices to be heard and acknowledged. Institutional members also hesitate to report instances of cheating or take appropriate action due to concerns about losing popularity among students, potentially damaging the reputation of the institution, airing internal issues publicly, as well as fear of legal consequences.

Sannia Perwaiz Iqbal *(Corresponding Author)*
Assistant Professor, Department of Medicine
Bahria University Health Sciences, Campus Karachi
Email: sanniapi@gmail.com

Received: 10-09-2023
Accepted: 30-09-2023

Unfortunately, this reluctance sends the wrong message to academicians, who quickly learn that they can evade consequences for engaging in misconduct.[12]

Institutions must prioritise the promotion of academic integrity and establish a culture where cheating is not tolerated. This can be achieved through clear policies and guidelines, effective communication with faculty and students, and the administration's assurance of full support for implementing a zero-tolerance policy on cheating. Workshops should be conducted to enhance students' ethical decision-making skills and remind them of the consequences of academic misconduct. Implementing assessment security measures, such as exam proctoring and restrictions on electronic devices, can enhance evaluation integrity.

Maintaining the integrity of exams can also involve reshuffling questions and ensuring adequate spacing between students. As medical education moves towards competency-based training and assessment, clinical evaluations like mini CEX assessments can monitor students' skills at different stages of their studies. Creating a transparent and fair environment, establishing clear standards for acceptable behavior, and prioritising learning over assessment contribute to reducing academic misconduct. Involving medical students in peer review processes and fostering a culture of academic integrity are important as well. Faculty members and administrators serve as role models for students, and their adherence to ethical practices has a positive impact. They should follow institutional policies and exhibit ethical behaviour in their scientific endeavors, earning the respect of students. Instances of academic misconduct by faculty and administrators must be promptly and fairly addressed. Motivating and encouraging students to uphold ethical principles is crucial in creating a healthy academic environment where those engaged in misconduct are excluded. Alongside knowledge and skills, a good medical professional must uphold high ethical and moral standards. By proactively addressing academic dishonesty, institutions can maintain the integrity of their educational programs and better prepare students for their professional lives. It should be made clear to all stakeholders, including students, faculty, staff, and administrators, that dishonesty has no place in medicine.

Authors Contribution:
Sannia Perwaiz Iqbal: Idea conception, write up

REFERENCES:

1. Tee S, Curtis K. Academic misconduct - Helping students retain their moral compass. Nurse Educ Today. 2018;61:153-154. doi: 10.1016/j.nedt.2017.11.030. Epub 2017 Dec 2.
2. Tiffin PA, Sanger E, Smith DT, Troughton A, Paton LW. Situational judgement test performance and subsequent misconduct in medical students. Med Educ. 2022;56(7):754-763. doi: 10.1111/medu.14801. Epub 2022 Mar 18.
3. Dar UF, Khan YS. Self-Reported Academic Misconduct among Medical Students: Perception and Prevalence. ScientificWorldJournal. 2021;2021:5580797. doi: 10.1155/2021/5580797.
4. Memon AR, Ali Awan MM. Higher education needs more improvement: The case of Pakistan. J Pak Med Assoc. 2017;67(5):821.
5. Hafeez K, Laiq-Uz-Zaman Khan M, Jawaid M, Haroon S. Academic misconduct among students in medical colleges of Karachi, Pakistan. Pak J Med Sci. 2013;29(3):699-702. doi: 10.12669/pjms.293.3300.
6. Mubeen SM; Qurrat-ul-Ain; Ghayas R, Adil Rizvi SH, Khan SA. Knowledge of scientific misconduct in publication among medical students. Educ Health (Abingdon). 2017;30(2):140-145. doi: 10.4103/efh.EfH_221_16.
7. Gadit AA. Plagiarism: how serious is this problem in Pakistan? J Pak Med Assoc. 2006;56(12):618.
8. Babu TA, Joseph NM, Sharmila V. Academic dishonesty among undergraduates from private medical schools in India. Are we on the right track? Med Teach. 2011;33(9):759-61. doi: 10.3109/0142159X.2011.576717. Epub 2011 May 19.
9. Kusnoor AV, Falik R. Cheating in medical school: the unacknowledged ailment. South Med J. 2013;106(8):479-83. doi: 10.1097/SMJ.0b013e3182a14388.
10. Calhoun T, Wood BD. Reporting academic misconduct. Radiol Technol. 2010;81(6):602-5.
11. Ghias K, Lakho GR, Asim H, Azam IS, Saeed SA. Self-reported attitudes and behaviours of medical students in Pakistan regarding academic misconduct: a cross-sectional study. BMC Med Ethics. 2014;15:43. doi: 10.1186/1472-6939-15-43.
12. Abdulghani HM, Haque S, Almusalam YA, Alanezi SL, Alsulaiman YA, Irshad M, Shaik SA, Khamis N. Self-reported cheating among medical students: An alarming finding in a cross-sectional study from Saudi Arabia. PLoS One. 2018;13(3):e0194963. doi: 10.1371/journal.pone.0194963.

Original Article **Open Access**

Comparison of Intravenous Dexmedetomidine and Tramadol for Management of Post-Spinal Anesthesia Shivering in Obstetric Cases

Shais Talat, Saqib Islam, Abdul Hameed Bhatti, Khalid Mehmood, Adam Talat, Najaf Imtiaz

ABSTRACT

Objective: The objective of this study is to compare the efficacy of dexmedetomidine and tramadol in controlling post-spinal anesthesia shivering in female patients after cesarean section.

Study Design and Setting: Quasi-experimental Study. Anesthesia Department of Combined Military Hospital, Thal from October 2022-March 2023.

Methodology: This study was conducted in ASA I and II patients aged 18-45. Sixty patients were enrolled for the study, who were divided into two group, group D received Inj dexmedetomidine (0.5mcg/kg) while group T received Inj Tramadol (0.5mg/kg). Time from injection of drug to cessation of shivering was recorded. End point of study was 30 mins after entry of patient in Post Anesthesia Care Unit (PACU).

Results: The study found that both drugs were effective in preventing shivering, but dexmedetomidine had a faster onset of action and a longer duration of action than tramadol. Mean time of cessation of shivering in both groups was calculated. In group D mean time of cessation was 2.9 ±0.9 while in group T it was 3.75 ±0.9. P-value was found to be highly significant 0.001.

Conclusion: The study concludes that dexmedetomidine is a more effective and safer alternative to tramadol for management of shivering in patients undergoing lower segment cesarean section under spinal anesthesia.

Key Words: Dexmedetomidine, shivering, tramadol

How to cite this Article:
Talat S, Islam S, Bhatti AH, Mehmood K, Talat A, Imtiaz N. Comparison of IV Dexmedetomidine and Tramadol for Management of Post-Spinal Anesthesia Shivering in Obstetric Cases. J Bahria Uni Med Dental Coll. 2023;13(4):250-4 DOI: https://doi.org/10.51985/JBUMDC2023221

INTRODUCTION:

Shivering is a common complication of intrathecal block.

Shais Talat *(Corresponding Author)*
Consultant, Department of Anaesthesiology
National University of Medical Sciences
Email: muhammadshais1991@gmail.com

Saqib Islam
Consultant, Department of General Surgeon
National University of Medical Sciences
Email: amcolian2523@gmail.com

Abdul Hameed Bhatti
Consultant, Department of Anaesthesiology
National University of Medical Sciences
Email: drahbhatti@gmail.com

Khalid Mehmood
Consultant, Department of Anaesthesiology
National University of Medical Sciences
Email: khalid1224@gmail.com

Adam Talat
Consultant, Department of General Surgeon
National University of Medical Sciences
Email: adam1992@gmail.com

Najaf Imtiaz
Consultant, Department of Anaesthesiology
National University of Medical Sciences
Email: najafimtiaz.ni@gmail.com

Received: 20-07-2023
Accepted: 18-09-2023

Incidence of shivering postoperatively as reported in literature is about 50-60%.[1] Shivering is distressing for the patient and leads to anxiety, pain increased oxygen consumption, increased intraocular and intragastric pressure and produce artifacts during monitoring.[2] As advancements in medical practices continue to evolve, the management of shivering in postoperative patients, particularly those undergoing cesarean sections, remains a pertinent challenge. The physical and psychological ramifications of shivering extend to both the immediate well-being of the patient and their overall postoperative experience. Understanding the multifactorial nature of shivering and exploring innovative solutions is essential to improve patient outcomes.

Different theories have been proposed to explain the mechanisms underlying shivering. Pain, loss of heat, postoperative increased sympathetic tone and release of pyrogens have been described in literature.[2] Regional anesthesia is associated with greater heat loss than general anesthesia resulting in increased postoperative shivering as reported by Koay et al.[3] Reason for this include cold crystalloid infusion, vasodilation and loss of shivering in area of block.

Different methods are used for prevention and treatment of shivering. Non-pharmacological methods include warming blankets, forced air warmers and use of warm crystalloids

infusion. Common pharmacological methods include pethidine, tramadol, ketamine, and clonidine.[4] Tramadol is an opioid agonist which works by inhibition of serotonin reuptake and norepinephrine in CNS. It is commonly used drug for control of post spinal anesthesia shivering. Tramadol is effective for control of shivering but at the same time it causes nausea and vomitingwhich is a cause of distress for mothers and hinders the early feeding and bonding with the neonate.[5]

Dexmedetomidine is a centrally acting alpha 2 receptor agonist and is gaining popularity and acceptance in ICU and OT setup because of its sedative and anxiolytic properties. It also decreases shivering threshold.[6] Dexmedetomidine has been evaluated as an agent for terminating shivering in several studies.[7] Mittal et al has found dexmedetomidine to be superior to tramadol with better hemodynamic stability and less side effects than tramadol in patients operated under spinal anesthesia.[8] Sedation, bradycardia and dry mouth are commonly reported side effects with it.

Most of the patient population in our setup consist of mothers coming for cesarean section and tramadol was commonly used but it was associated with frequent nausea and vomiting which caused much distress to mothers. The increasing prevalence of cesarean section deliveries in recent years further underscores the significance of this study. As this procedure becomes more commonplace, it is crucial to refine perioperative practices to ensure the well-being of both mothers and newborns. In an era where patient-centric care and personalized medicine are gaining prominence, tailoring our approach to postoperative shivering management is in line with the broader objective of optimizing healthcare outcomes. Consequently, our research strives to contribute to this paradigm shift by offering a novel perspective on shivering control, acknowledging the unique needs and challenges faced by mothers undergoing cesarean sections. By addressing shivering and its side effects in this specific patient population, we aim to enhance not only the physical recovery of the mother but also her ability to engage in the critical early moments of bonding and nurturing her newborn. We evaluated the effectiveness of dexmedetomidine and compared it with tramadol for preventing shivering in caesarean section patients. We assessed the time to cessation of shivering, compared adverse events, and evaluated hemodynamic stability. We have found a lack of research in this patient population regarding the use of dexmedetomidine as an anti-shivering agent. By doing so, we tried fill the gap in the literature and provide an alternative into the optimal treatment for shivering in this patient population.

METHODOLOGY:

This Quasi-experimental Study was conducted in tertiary care hospital setting of Combined Military Hospital Thal Operation theater after approval from independent local hospital ethical review committee via ERC No.04/09/22(38) from October 2022 to March 2023.

Sample size was calculated[9] considering expected difference between two group means of 150s with expected standard deviation of 180s. Power of test was set to 80% with level of significance of 5%. Sample size came out 23 in each group but we took 30 participants in each group to decrease bias and improve results.[9] Total sample size was 60.

ASA I and II patients between the ages of 18 and 45 who were scheduled for elective lower segment cesarean section under spinal anesthesia were enrolled in the study after being briefed and providing written informed consent. The study included patients who were hemodynamically stable with no known comorbidities.

Patients coming for emergency surgery, those with pyrexia, history of allergy to dexmedetomidine or opioids, hypovolemia, premedication, heart blocks, or bradycardia were excluded from study.

Patients who developed shivering during or 30 minutes after the cesarean section were uniformly divided into two groups by non-probability consecutive sampling to receive either intravenous dexmedetomidine (0.5mcg/kg) diluted to 1mcg/ml (Group D) or intravenous tramadol (0.5mg/kg) diluted to 1mg/ml (Group T). The primary outcome which was observed was time from the injection of the drug to cessation of shivering. If shivering recurred after initial cessation, a second dose of the allocated drug was administered. The study endpoint was 30 minutes after entry of the patient in the post anesthesia recovery unit.

Operation theater was warmed to a temperature of 24°C before patient was brought in and was maintained throughout the operation. Standard ASA monitoring was applied including pulse oximeter, non-invasive BP, ECG, and temperature probe. All patients were given infusion of warm Ringer lactate solution (22-24°C) 10ml/kg with an 18G IV cannula. The medications and anesthetics administered to the patients were not heated and there were no additional methods used to warm the patients. Furthermore, the patients did not receive any premedication. Spinal Anesthesia was given to all patients with 25G or 27G Quincke Spinal needle in L3-L4 or L2-L3 interspace in sitting position and Inj Bupivacaine 0.5%, 12-15mg was injected in subarachnoid space. Sensory level of anesthesia was confirmed using alcohol-soaked gauzes using Bromage scale (0 = block not present, 1 = only hip blocked, 2 = both hip and knee blocked, 3=all three hip, knee and ankle blocked).[10] All operations were performed by consultant gynecologist. Vitals of patients were monitored and charted every 5 mins intraoperatively. Temperature of the patient was recorded with probe applied to axilla. Oxygen was given with simple face mask throughout the surgery. OT nurse designated to the case monitored the patient for development of shivering intraoperatively and postoperatively in PACU.

Wrench classification[11] of shivering was used which divides shivering into five grades: Grade 0, which means no shivering was observed; Grade 1, which indicates that there was no visible muscle activity but the patient had cyanosis or piloerection; Grade 2, which means only one muscle had activity; Grade 3, which means that more than one muscle had activity; and Grade 4, which means that the whole body had muscle activity.[11] Patients who experienced Grade 3 or Grade 4 muscle activity were considered in the analysis, as subjective method was used to evaluate shivering.

Patients with shivering were given either of the two drugs slow IV by attending anesthesiologist and the time shivering started and ended were noted. Total time of the operation, duration of spinal anesthesia, occurrence of unpleasant experiences like nausea, vomiting, heart rate of less than 50 beats per minute, decrease in MAP of more than 15% from baseline, and dizziness were documented.

The data, recorded on proforma was transferred to SPSS 25.0 (version for windows) for statistical analysis. Descriptive statistics were used to summarize the data, with qualitative data expressed as percentages and frequency and quantitative data expressed as mean ± standard deviation. T-test was used to analyze the variations in continuous variables between the two groups, while the chi-square test was utilized to examine the differences in categorical variables. Statistical significance was considered at p = 0.05.

RESULTS:

Total 60 patients were included in the study, 30 in each group which met the inclusion criteria. Groups were comparable according to their ages.

In Group D; Mean Age was 30.33 ± 9.1 years (minimum was 19 and maximum was 42 years). 70% cases had Grade 2 shivering, 10% cases had Grade 3 shivering, and 20% cases had Grade 4 shivering. Table-1. Mean time of cessation of shivering was 2.9 ± 0.9 (minimum was 1.5 minutes and maximum were 4.5 minutes). Table-2

In Group T; Mean Age 32.5 ± 6.8 years (minimum was 19 and Maximum was 42 years). 33.3% cases had Grade 2 shivering, 30% cases had Grade 3 shivering, and 36.7% cases had Grade 4 shivering. Table-1. Mean time of cessation of shivering was 3.7 ± 0.9 (minimum was 2.5 minutes and maximum were 5.5 minutes). Table-2 Second episode of shivering was observed in 33.3% cases in group receiving tramadol while in dexmedetomidine group it was observed to be 16.7%. However, the difference was not found to be statistically significant. Table-3

Stratification of cessation time of shivering with regards to age groups was done. P–value in Group-D was 0.29 and in Group-T was 0.32. Comparison of means of Age in both groups was done and p-value was found to be 0.29. Comparison of means of cessation time of shivering in both groups was done and p-value was found to be highly significant (0.0004). Table-2

Table 1: Distribution of grade of shivering in study cases (n = 60)

Grades of shivering	Group D (n=30)	
	Frequency	**Percentage**
02	21	70
03	03	10
04	06	20
Total	30	100
Grades of shivering	Group T (n=30)	
	Frequency	**Percentage**
02	10	33.3
03	09	30
04	11	36.7
Total	30	100

Table 2: Time of cessation of shivering in study cases (n=60)

	Group D (n=30)	**Group T** (n=30)	**p-value**
Mean	2.9	3.75	0.001
SD	0.9	0.9	

Table 3 : Distribution of second episode of shivering in study cases (n=60)

Second episode of shivering	Group D (n=30)		**p-value**
	Frequency	**Percentage**	
Yes	05	16.7	**0.136**
No	25	83.3	
Total	30	100	
Second episode of shivering	Group D (n=30)		**p-value**
	Frequency	**Percentage**	
Yes	10	33.3	**0.136**
No	20	66.7	
Total	30	100	

DISCUSSSION:

Experiencing shivering during surgery under regional anesthesia can be an uncomfortable and distressing ordeal for the patient. Shivering can be attributed to various factors, such as disruptions in central thermoregulation, vasodilation leading to internal heat redistribution, and heat loss to the surrounding environment.[12] Shivering is not only uncomfortable for the patient but it also causes many of the adverse outcomes like increase oxygen consumption, increase heart rate, increase CO2 production and increase lactic acid production.

Mechanism of post-operative shivering is not proven yet but multiple theories exist which fixes the cause on heat loss to environment, problem with central thermoregulation and heat redistribution.[13] Risk factors identified for shivering include age, temperature of environment, temperature of drugs and block level.[14]

Tramadol is an agent which is used most commonly for

shivering.[15] It is an opioid which acts on ì receptor with some activity on kappa and delta receptors. The mechanism by which tramadol ends shivering is via its opioid or noradrenergic activity. It is associated with multiple side effects including nausea and vomiting which is cause of distress in obstetric population.[16,17]

Dexmedetomidine is alpha 2 receptor agonist which is used as antihypertensive, analgesic, sedative and anti-shivering agent.[18,19] Dexmedetomidine can terminate shivering via inhibition of alpha 2 mediated adenyl cyclase in CNS and causing vasoconstriction. Moreover it can regulate hypothalamic regulatory activity.[20] Dexmedetomidine acts centrally and decrease the vasoconstriction and threshold for shivering comparatively.[21] Dexmedetomidine is gaining popularity in ICUs and OT and is being used for sedation of patients on ventilatory support, procedural sedation and as an adjunct to local anesthetics. Our study primarily focuses on patients undergoing cesarean section under spinal anesthesia as incidence of shivering in this population is almost 67.5%.[22] Mittal et al has reported a success rate of 100% with dexmedetomidine when used as an anti-shivering drug.[8] These results depict the success of dexmedetomidine as a superior anti shivering agent in different patients group. However, there was a gap with little evidence available for use of intravenous dexmedetomidine in healthy obstetric population which this study aims to fill.

We found that intravenous dexmedetomidine in a dose of 0.5 mcg/kg is a superior anti shivering agent as compared to tramadol with no effects on hemodynamic status and significantly less side effects.

Hypotension, sedation and bradycardia are the side effects reported in literature with dexmedetomidine however with the dose of 0.5 mcg/kg no such side effects were observed.[23] In our study 30 patients who received dexmedetomidine did not develop hypotension with MAP less than 60mmhg requiring vasopressors, bradycardia was observed after administration, but heart rate did not go below 50 beats per minute. Recurrence of shivering after one dose of tramadol was found to be 33.3% in tramadol group as compared to 16.7 in dexmedetomidine group but it was not found to be statistically significant and further studies with a large sample size is needed to prove this relationship.

Authors Contribution:
Shais Talat: reviewed all the cases for inclusion, data collection, statistical analysis, drafted this article
Saqib Islam: conceptualized and supervised the study, reviewed all the cases for inclusion, critically reviewed the manuscript
Abdul Hameed Bhatti: Data Collection
Khalid Mahmood: Data Collection
Adam Talat: Data Collection
Nafaz Imtiaz: Conceptualized and supervised that study.

REFERENCES:

1. Golmohammadi M, Karami N, Tahmasebi R. Incidence of Shivering During Cesarean Section in Patients under Spinal Anesthesia with or without Fentanyl. Studies in Medical Sciences. 2020;31(6):423-32.
2. Lopez MB. Postanaesthetic Shivering – from Pathophysiology to Prevention. Romanian Journal of Anaesthesia and Intensive Care. 2018;25(1):73-81 DOI: https://doi.org/10.21454 /rjaic.7518.251.xum.
3. Koay CK, Chan WY, Chin M-K. Shivering During Regional Anaesthesia and Its Control with Pethidine. Singapore medical journal. 1991;32 3:160-2.
4. Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy Spectrum of Antishivering Medications: Meta-Analysis of Randomized Controlled Trials. Crit Care Med. 2012;40(11): 3070-82 DOI: https://doi.org/10.1097/ CCM. 0b013e 31825b931e.
5. Ng KFJ, Tsui SL, Yang JC, Ho ET. Increased Nausea and Dizziness When Using Tramadol for Post-Operative Patient-Controlled Analgesia (Pca) Compared with Morphine after Intraoperative Loading with Morphine. European journal of anaesthesiology. 1998;15 5:565-70 DOI: https://doi.org/ 10.1046 /j.1365-2346.1998.00354.x.
6. Li Y-Z, Jiang Y, Lin H, Yang X-P. Subarachnoid and Epidural Dexmedetomidine for the Prevention of Post-Anesthetic Shivering: A Meta-Analysis and Systematic Review. Drug design, development and therapy. 2019:3785-98 DOI: https://doi.org/10.2147/DDDT.S204411.
7. Botros JM, Mahmoud AMS, Ragab SG, Ahmed MAA, Roushdy HMS, Yassin HM, et al. Comparative Study between Dexmedetomidine and Ondansteron for Prevention of Post Spinal Shivering. A Randomized Controlled Trial. BMC anesthesiology. 2018;18:1-8 DOI: https://doi.org/10.1186 /s12871-018-0640-3.
8. Mittal G, Gupta K, Katyal S, Kaushal S. Randomised Double-Blind Comparative Study of Dexmedetomidine and Tramadol for Post-Spinal Anaesthesia Shivering. Indian J Anaesth. 2014;58(3):257-62 DOI: https://doi.org/10.4103/0019-5049.135031.
9. Dhand N, Singh M. Sample Size Calculator for Comparing Two Independent Means.
10. Singh A, Gupta A, Datta PK, Pandey M. Intrathecal Levobupivacaine Versus Bupivacaine for Inguinal Hernia Surgery: A Randomized Controlled Trial. Korean Journal of Anesthesiology. 2018;71(3):220-5 DOI: https://doi.org/10.4097 /kja.d.18.27191.
11. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AWA. The Minimum Effective Doses of Pethidine and Doxapram in the Treatment of Post-Anaesthetic Shivering. Anaesthesia. 1997;52(1):32-6 DOI: https://doi.org/10.1111/j.1365-2044.1997.006-az006.x.
12. Lopez MB. Postanaesthetic Shivering–from Pathophysiology to Prevention. Romanian journal of anaesthesia and intensive care. 2018;25(1):73.
13. De Witte J, Sessler Daniel I. Perioperative Shivering: Physiology and Pharmacology. Anesthesiology. 2002;96(2) :467-84 DOI: https://doi.org/10.1097/00000542-200202000-00036.

14. Wódarski B, Chutkowski R, Banasiewicz J, Moorthi K, Wójtowicz S, Malec-Milewska M, et al. Risk Factors for Shivering During Caesarean Section under Spinal Anaesthesia. A Prospective Observational Study. Acta Anaesthesiologica Scandinavica. 2020;64(1):112-6 DOI: https://doi.org/10.1111 /aas.13462.

15. Yaakop AF, Hassan MH, Omar SC, Mazlan MZ, Mukmin LA, W. Hassan WN. Tramadol Vs. Pethidine to Control Perioperative Shivering in Cesarean Section under Spinal Anesthesia: A Double-Blind Study. Anaesth Pain Intensive Care. 2022;26(3):283-90 DOI: https://doi.org/ 10.35975/ apic.v26i3.1893.

16. Reddy V, Chiruvella S. Clonidine Versus Tramadol for Post Spinal Shivering During Caesarean Section: A Randomized Double Blind Clinical Study. Journal of Obstetric Anaesthesia and Critical Care. 2011;1(1):26-9 DOI: https://doi.org/ 10.4103/ 2249-4472.84252.

17. Ng KF, Tsui SL, Yang JC, Ho ET. Increased Nausea and Dizziness When Using Tramadol for Post-Operative Patient-Controlled Analgesia (Pca) Compared with Morphine after Intraoperative Loading with Morphine. Eur J Anaesthesiol. 1998;15(5):565-70 DOI: https://doi.org/10.1046/j.1365-2346.1998.00354.x.

18. Salarian S, Taherkhanchi B, Dabbagh A, Darban M, Bagheri B. Dexmedetomidine Mechanism of Action: An Update. Journal of Cellular & Molecular Anesthesia. 2016;1(2):91-4 DOI: https://doi.org/10.22037/jcma.v1i2.11398.

19. Grewal A. Dexmedetomidine: New Avenues. J Anaesthesiol Clin Pharmacol. 2011;27(3):297-302 DOI: https://doi.org/10.4103 /0970-9185.83670.

20. Miao S, Shi M, Zou L, Wang G. Effect of Intrathecal Dexmedetomidine on Preventing Shivering in Cesarean Section after Spinal Anesthesia: A Meta-Analysis and Trial Sequential Analysis. Drug Design, Development and Therapy. 2018:3775-83.

21. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine Does Not Alter the Sweating Threshold, but Comparably and Linearly Decreases the Vasoconstriction and Shivering Thresholds. Anesthesiology. 1997;87(4):835-41 DOI: https://doi.org/10.1097/00000542-199710000-00017.

22. Sachidananda R, Basavaraj K, Shaikh SI, Umesh G, Bhat T, Arpitha B. Comparison of Prophylactic Intravenous Magnesium Sulfate with Tramadol for Postspinal Shivering in Elective Cesarean Section: A Placebo Controlled Randomized Double-Blind Pilot Study. Anesth Essays Res. 2018;12(1):130-4 DOI: https://doi.org/10.4103 /aer. AER_ 196_17.

23. Reel B, Maani CV. Dexmedetomidine: StatPearls Publishing, Treasure Island (FL); 2022.

Original Article **Open Access**

Health-related Quality of Life in Pediatric and Adolescent Patients with Transfusion Dependent ß-Thalassemia

Hina Qayyum, Shamama Hasan, Samra Akram, Amarah Ghani, Areeba Sohail, Annowish Nasir

ABSTRACT

Objective: To evaluate the impact of disease on physical, educational, psychological and social wellbeing of transfusion dependent thalassemia major patients.

Study Design and Setting: A case control study conducted in Thalassemia Centre of Pediatric Ward, PNS Shifa Hospital Karachi for a duration of six months from March 2019 till August 2019.

Methodology: Seventy cases of thalassemia major patients were enrolled along with a control group of hundred patients. The enrolled cases were registered thalassemia patients of pediatric hematology clinic. The controls are healthy, age and sex matched participants and their history was taken to compare with the diseased participants. Peds QL4.0 generic core scale proforma was filled to assess health related quality of life (HRQoL) in these patients.

Results: Mean age of patients was 8.56 ± 4.526 and 7.94 ± 4.528 for controls. The greatest level of difficulty was seen in thalassemia patients in physical functioning, health activities and emotional functioning domains with a score of 9.4 ± 6.85, 9.186 ± 5.724 and 6.4 ± 3.5 respectively. The total score in terms of increasing difficulty was 51.84 ± 21.26 in patients while it was 15.06 ± 10.26 in control group with a significant difference (p = 0.05). There was also significant association of splenectomy with health-related scores.

Conclusion: This study reiterated the impact of blood transfusion, iron chelation and other clinical dependencies of thalassemia major patients on their quality of life. The questionnaire data provided valuable information regarding impact on daily life activities and its difference in comparison to controls.

Keywords: Thalassemia major, Transfusion-dependent, Quality of life

How to cite this Article:
Qayyum H, Hasan Sm Ajran S, Ghani A, Sohail A, Nasir A. Health-related Quality of Life in Pediatric and Adolescent Patients with Transfusion Dependent ß-Thalassemia. J Bahria Uni Med Dental Coll. 2023;13(4):255-60 DOI: https://doi.org/10.51985 /JBUMDC202248

Hina Qayyum *(Corresponding Author)*
Assistant Professor, Department of Paediatrics
HBS Medical and Dental College Islamabad
Email: hinaqaayum@gmail.com

Shamama Hasan
Assistant Professor, Department of Pediatric Gastroenterology
Pak Emirates Military Hospital/National University Of Medical Sciences (NUMS) Rawalpindi
Email: shamamahasan2014@gmail.com

Samra Akram
Resident, Department of General Surgery
Punjab Rangers Teaching Hospital Lahore
Email: samra.winx98@gmail.com

Amarah Ghani
Resident, Department of General Surgery
Indus Hospital Karachi
Email: amarahghanishaikh@gmail.com

Areeba Sohail
Registrar, Department of Emergency Medicine
Al-Sabah Hospital, Kuwait
Email: Areebahsohail@yahoo.com

Annowish Nasir
Medical Officer
Agha Khan Hospital Karachi
Email:annowish.nasir@gmail.com

Received: 11-04-2022
Accepted: 01-09-2023

INTRODUCTION:

Thalassemia is one of the most common genetic disorders of hemoglobin production worldwide. There are various conventional therapies used for the treatment of patients with thalassemia major. However, there are certain limitations and drawbacks of these treatment modalities. A better understanding of underlying pathophysiology of thalassemia has led to the development of newer treatment options which are mainly focused on correction of imbalance between different types of globin chains, decreasing ineffective erythropoiesis and reducing iron overload by using iron chelation. This will ultimately result in a better outcome in transfusion dependent thalassemia patients in terms of their life expectancy, symptom control and better adherence to treatment plan.[1] Management of thalassemia major patients still revolve around regular and life-long blood transfusion therapy.[2] There are many challenges faced by these patients such as limited access to regular and safe blood transfusions, inadequate voluntary blood donors as well as lack of national blood policies, poor thalassemia awareness at community and institutional level. Transfusion related infections are also very commonly seen in these patients. All these factors result in decreased health related quality of life in thalassemia patients. These factors are particularly challenging in resource

poor countries where mortality and morbidity is significantly higher due to complications of disease as well as treatment. This includes cardiac complications like cardiomyopathy, liver problems like chronic hepatitis. Endocrine problems involving pancreas can result in diabetes mellitus, thyroid gland involvement result in hypothyroidism, gonadal involvement cause pubertal delay, spleen enlargement result in mechanical discomfort and increased demand for trànsfusion and stunted growth.[3]

Thalassemia is the most prevalent genetic blood disorder in the world according to World Health Organization (WHO), found in more than 60 countries with a carrier population of up to 150 million.[4] It is highly prevalent among children in South Asia, Mediterranean region and Middle East. In Pakistan, thalassemia is highly prevalent with a â thalassemia gene frequency of 5% to 8% and almost 500 new cases are diagnosed each year.[5,6]

The quality of life of a thalassemia major patient depends upon various factors i.e., the number of transfusions they need, their age, quality of treatment they are getting, social skills, growth pattern, and other socioeconomic factors. Yasmeen H also highlighted the impact of these factors on life quality of thalassemia major patients in Pakistan.[7] With the passage of time, when the age of the patient increases, health complications also start increasing and adversely affect their life.[8] These challenges and difficulties include social issues, school performance of children, psychological issues, difficulty in expressing their feelings and due to physical illness, they remain unable to perform well at academics.[9]

Health related quality of life (HRQoL) measurement is a multi-dimensional concept that focuses on the impact of disease and its treatment on the health and well-being of individuals. Varni et al constructed the multidimensional PedsQL 4.0 questionnaire to measure the essential core domains for paediatric HRQoL: Physical functioning, Emotional functioning, and social functioning, as delineated by the World Health Organization (WHO), as well as School functioning.[10]

This study aims to evaluate the complications faced by thalassemia major patients in their daily life and the impact of clinical management within different age groups of patients. Assessment of level of difficulty will help us highlight the importance of comprehensive management planning by involving school representatives, family and physicians to help these patients lead a better life.

METHODOLOGY

After receiving the ethical approval from the Ethical Review Committee, Bahria University Medical and Dental College Karachi (ERC 58/2018), the consent of included patients and controls was taken. The cases were recruited through consecutive sampling over the specified period of time. This case control study was performed at Thalassemia Centre of Pediatric Ward at PNS Shifa Hospital, Karachi. The study duration was six months from March 2019 to August 2019. A total of 70 cases of thalassemia major patients and 100 controls of same age and sex were included. Thalassemia major children fulfilling the following criteria were included: having an age range between 2 and 18 years, receiving a blood transfusion on a monthly or near-monthly basis. Patients suffering from any acute infection and those thalassemia patients who had any chronic condition not related to thalassemia or its complications, were excluded to avoid its impact on results. For all enrolled patients, full data was taken about their disease history including transfusion requirement and splenectomy. HRQoL was assessed with the PedsQoL 4.0 Generic Core Scales. This instrument has 23-items that are designed to measure the core dimensions of health as delineated by WHO. The PedsQoL 4.0 encompasses the essential core domains for pediatric HRQoL measurement: 1) Physical functioning (8 items), 2) Emotional functioning (5items), 3) Social functioning (5 items) and 4) School functioning (5 items). It consists of developmentally appropriate forms for ages 2–4, 5–7, and 8–12 and 13–18 years. The reliability, validity, responsiveness, and practicality of the PedsQoL Generic Core Scales have been assessed in both physically healthy pediatric populations and in pediatric acute and chronic health conditions. The internal consistency reliability of the PedsQoL 4.0 Generic Core Scale approached 0.90 for self-report. The validity of the PedsQoL Generic Core Scales has been demonstrated through known group comparisons and correlations with other measures of disease burden. User agreement was signed with MAPI Research Institute, Lyon, France prior to using the questionnaires.

The obtained data was computed and analyzed by SPSS (Statistical Package for the Social Sciences) program version 19.0. General characteristics of the patients were presented in terms of percentage, mean, and standard deviation and median for data not normally distributed. For QoL, both total HRQoL score and physical, emotional, social, school achievement and psychological scores were presented in terms of mean and standard deviation. One way ANOVA, and t-test were used to examine the relationship between HRQoL and each demographic/clinical data.

RESULTS:

Total 170 individuals were enrolled in this study, among which 70 were cases (diseased children) and 100 controls (healthy children, age and sex matched). Among cases, 36 (51.4%) were male and 34(48.6%) were female. While in controls, 48 (48%) were male and 52 (52%) females. Mean age was 8.56 ± 4.526 for cases and 7.94 ± 4.528 for controls. Mean physical functioning score, emotional functioning score, social functioning score, school functioning score, health & activities score, feelings score, getting along with others and school scores were 9.4 ± 6.85, 6.4 ± 3.5, 4.5 ± 3.63, 6.086 ± 4.149, 9.186 ± 5.724, 6.314 ±3.304, 4.457

±3.63, 5.50 ± 4.42 for cases and 3.01 ± 4.734, 2.14 ± 1.77,1.25 ± 1.77, 2.06 ± 2.019, 1.27 ± 2.107, 1.54 ± 1.935, 1.27 ± 2.201, 2.52 ± 3.23 for controls respectively (Figure 1) and have significant effect with p = 0.05. The total score was 51.84 ± 21.26 in patients while it was 15.06 ± 10.26 in control group with a significant difference (p = 0.05).

There were no significant differences between gender of children and all health quality scores (p= 0.05). There was significant effect of school functioning and school scores among (2-4) and (5-7) age groups with p = 0.05 (Figure 2). The impact of thalassemia on various health domains was studied within different levels of education and economic groups, but no significant relationship was found (p-value<0.05) (Table 1)

Similarly, all health scores were analyzed with type of Thalassemia (none, major, intermediate and minor), it was observed that all scores were significant (p = 0.05) in none and major groups and insignificant (p= 0.05) in intermediate and minor except emotional and physical scores. There were insignificant association of blood groups and number of transfusions with quality-of-life scores except social score, health activity, feelings and getting along score for =3 transfusions and also significant association of splenectomy with health-related scores. (Table 2)

Figure 1: QOL score in thalassemia children and healthy controls

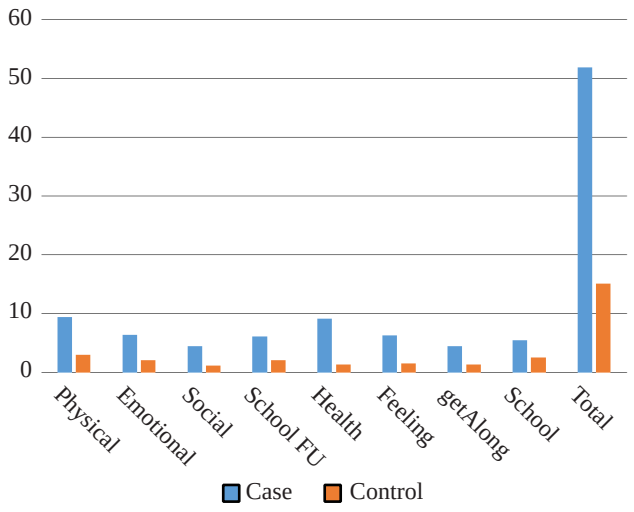
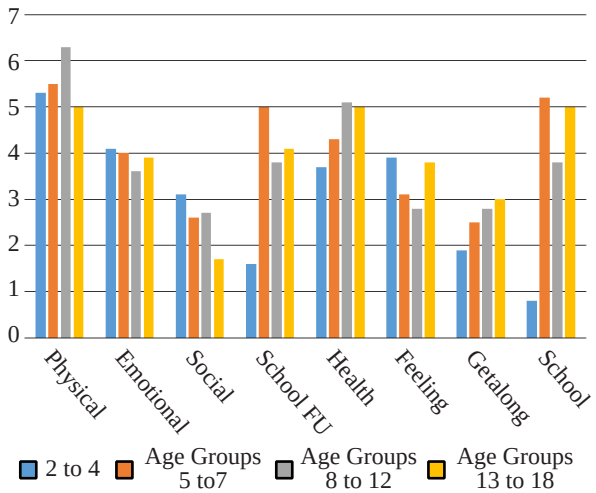


Figure 2: Comparison between different scores regarding age groups



DISCUSSION:

Thalassemia major is characterized by the lack of production of hemoglobin chains. It is also categorized under hemoglobinopathies. The management therapy i.e., blood transfusion leads to many side effects like cardiac disease, iron overload and endocrinopathies. With the passage of time, the consumption of blood starts increasing because of over destruction of blood cells in the spleen and increased needs of the body.[11] Repeated blood transfusions in these patients might result in transfusion related infections. A high prevalence of transfusion related infections like hepatitis B and C was observed in a study conducted in Balochistan, Pakistan.[12] Consequently, the quality of life of patients is compromised severely. A systematic review by Greco F found a low HRQoL in transfusion dependent patients in their physical, emotional and social functioning.[13]

The quality of life of thalassemia major patients was assessed on different parameters and they showed a higher level of difficulty in comparison to controls. A total of seventy interviews/surveys were conducted among the cases from age 2-18. The study found out that the complications of the disease are directly affecting the quality of life of patients and they feel limited in terms of expression.[14,15] The thalassemia major patients mostly remain out of schools and academic activities due to the complications of the disease and it was noticed from the survey that the majority of patients were out of school or didn't pursue their education.[16] A possible explanation can be the level of difficulty they face while getting along with other students and socializing with them. This possible reason was backed by the results obtained from the survey of the level of social skills and getting along.[17] A study by Abdel Hakeem GL found physical performance of thalassemia patients to be most affected in all the domains by using Peds QoL 4.0 scale.[18]

Mean age of our study population was 8.56 ± 4.526 for cases and 7.94 ± 4.528 for controls. Patients with splenectomy were found to be having great difficulty in their physical activities, social interaction and emotional status. They have to remain on antibiotic prophylaxis and follow precautions to remain infection free. Spleen is responsible for filtering blood, maintenance of immunity, and fighting against infections, so there are many risks associated with spleen removal in these individuals.[19]

Table 1: Comparison between different QOL scores regarding demographic data

	Parameters	Physical Score		Emotional Score		Social		School Function		Health & Activities		Feelings		Get Along		School	
		Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value
Gender	Male	5.393±6.17	0.624	4.08 ±3.22	.469	2.68 ±3.04	0.711	4.12 ± 3.80	0.158	4.702 ±5.603	0.691	3.89 ± 3.44	0.154	2.688 ± 3.22	0.706	4.20 ± 4.49	0.146
	Female	5.884±6.826		3.71 ±3.47		2.50 ±3.23		3.32 ± 3.49		4.36 ±5.60		3.13 ± 3.53		2.49 ± 3.331		3.30 ± 3.51	
Age Groups	2-4	5.324 ± 6.654	0.891	4.05 ±3.79	0.946	3.08 ±3.63	0.519	1.62 ± 2.84	0.0001	3.68 ±5.68	0.638	2.81 ±3.64	0.202	1.97±2.85	0.436	0.81±1.35	0.001
	5-7	5.521 ±6.432		4.0 ± 3.46		2.604 ± 3.14		5.02 ±4.37		4.27 ±5.81		3.8 ±3.63		2.54 ±3.64		5.19 ± 4.95	
	8-12	6.31 ±7.15	0.381	3.65±3.21	0.663	2.73±2.88	0.119	3.8±2.9	0.710	5.05± 5.45	0.986	3.71±3.39	0.752	2.78±3.09	0.733	3.78±3.14	0.138
	13-18	5.0 ±5.25		3.97 ±2.99		1.70±2.88		4.1±3.6		5.03±5.47		3.47±3.32		3.03±3.49		5.0±4.29	
Education	Class <1	6.42±8.17	0.717	3.83±3.43	0.78	2.83±3.36	0.87	6.4±4.06	0.323	4.25±6.41	0.87	3.0±2.34	0.40	1.67±2.23	0.35	5.5±2.9	0.98
	Class1-4	5.64±6.29		4.13±3.26		2.68±3.02		5.2±3.74		4.55±5.47		3.89±3.47		2.68±3.54		5.47±4.73	
	Class 5-10	4.3±5.5	0.92	2.8±2.3	0.14	1.5±2.2	0.16	3.8±2.7	0.67	3.7±4.6	0.73	2.7±2.8	0.14	2.0±2.8	0.06	4.6±3.8	0.66
	Class >10	4.5±5.2		4.4±4.1		2.9±4.1		4.3±4.6		4.4±5.7		4.4±3.5		4.1±3.5		5.3±3.6	
	No Schooling	6.6±7.1	0.42	4.4±3.9	0.98	3.2±3.5	0.79	1.6±2.9	0.31	5.2±6.3	0.73	3.7±4.1	0.68	2.9±3.5	0.35	0.89±1.5	0.001
Income	=30,000	6.3±6.6	0.204	4.0±3.5	0.68	2.9±3.4	0.245	3.7±3.6	0.86	4.4±5.5	0.83	3.6±3.5	0.66	2.6±3.4	0.97	3.6±4.3	0.66
	>30,000	5.1±6.4		3.8±3.2		2.3±2.9		3.8±3.7		4.6±5.7		3.4±3.5		2.6±3.2		3.9±3.8	

Table 2: Comparison between different QOL scores regarding type of thalassemia, blood group, transfusion requirement and status of splenectomy

Physical Score	Type of Thalassemia				Blood Groups						No of Transfusions					
	none	major	intermediate	minor	A +ve	B +ve	AB +ve	O +ve	B -ve	O -ve	None	1-3	4-6	>7	Yes	No
	3.01±4.7	9.5±6.9	13.0±5.6	2.3±1.2	5.3±6.3	6.1±7.2	6.7±6.6	4.9±5.6	2.5±0.71	14.5±2.12	3.01±4.7	2.3±1.15	13.9±6.5	9.2±6.7	12.2±7.9	5.4±6.3
p value	0.00		0.025		0.52		0.390		0.17		0.806		0.066		0.012	
Emotional Score	2.1±1.8	6.4±3.6	8.0±1.8	3.3±2.5	3.6±3.2	3.7±3.4	6.3±2.9	4±3.6	2.5±0.71	6.5±4.9	2.1±1.8	3.33±2.5	7.9±4.6	6.4±3.3	8.2±2.9	3.7±3.3
p value	0.00		0.035		0.89		0.70		0.375		0.257		0.251		0.001	
Social	1.3±1.8	4.4±3.7	6.8±1.3	4.0±3.5	2.3±2.8	2.7±3.06	4.2±3.6	2.2±3.5	2.0±2.8	5.0±7.1	1.25±1.8	4.0±3.5	8.3±2.5	4.02±3.5	6.2±3.3	2.5±3.1
p value	0.00		0.194		0.45		0.120		0.633		0.011		0.02		0.004	
School Function	2.06±2.0	6.3±4.2	5.3±3.8	3.3±2.3	2.9±3.3	3.91±3.7	5.3±5.3	4.1±3.6	5.0±1.4	7±4.2	2.1±2.1	3.3±2.3	6.4±4.1	6.2±4.2	4.7±4.8	3.7±3.6
p value	0.00		0.477		0.123		0.410		0.592		0.286		0.906		0.519	
Health & Activities	1.3±2.1	9.1±5.9	9.8±2.9	11.0±3.0	4.6±6.0	3.9±5.2	6.5±5.97	4.4±5.04	1.0±1.41	14.5±4.9	1.3±2.1	11±3.0	11.9±3.8	8.7±5.9	13.2±3.5	4.2±5.4
p value	0.00		0.6		0.51		0.260		0.066		0.00		0.152		0.00	
Feelings	1.5±1.9	6.3±3.4	6.0±1.6	6.3±0.57	3.2±3.5	3.4±3.5	4.5±4.6	3.8±3.04	2.5±0.71	8.0±5.6	1.5±1.9	6.3±0.58	7.4±1.5	6.2±3.5	6.8±3.7	3.4±3.4
p value	0.00		0.75		0.841		0.558		0.306		0.00		0.347		0.017	
Get Along	1.3±2.2	4.3±3.8	4.8±1.9	6.7±0.57	2.6±3.3	2.5±3.0	5.0±3.8	1.8±2.8	0±0	7.0±9.8	1.3±2.2	6.67±0.57	5.8±0.46	4.2±3.9	6.2±3.4	2.5±3.2
p value	0.00		0.16		0.827		0.005		0.423		0.00		0.257		0.006	
School	2.5±3.2	5.6±4.6	4.5±3.0	4.7±3.2	2.9±3.2	4.0±4.4	6.0±6.3	3.8±3.4	5.0±1.41	10±8.4	2.5±3.24	4.7±3.2	6.0±4.1	5.5±4.6	3.7±3.5	3.8±4.1
p value	0.00		0.95		0.100		0.141		0.497		0.26		0.758		0.961	

Patients with thalassemia major remain dependent on blood transfusions for life and also develop transfusion related complications.[20] There are multiple admissions for transfusion and increasing chelation requirement. This affects their physical functioning as well as educational process. Along with this, the emotional state was also found to be imbalanced in cases as compared to controls. The individuals with thalassemia find it difficult to express themselves.[21]

Thalassemia major patients have poor social skills than controls. They were found to have higher difficulty levels in getting along with the peers. The possible explanation for this can be their struggle with the disease and disturbed mental health.[22] Therefore, it is recommended to formulate a standard management program for thalassemia major patients. The thalassemia centers across the country should be developed and multidisciplinary teams should take care of the patients. This must include, in addition to the team of medical and surgical specialists, members from psychology, learning disability, dieticians as well as social services.

CONCLUSION:

This study shows that thalassemia major patients face many difficulties due to their lifelong dependency on transfusions. This burden of disease greatly impacts their life. Results of the study clearly show major differences in health-related quality of life between thalassemia patients and healthy individuals. Their life is affected uniformly in all domains of life such as social, physical, educational as well as emotional. Therefore, this study highlights the importance of more integrated planning for health services in our region.

Authors Contribution:
Hina Qayyum: Drafting the work, conception and design, critical revision
Shamama Hasan: Revising the work critically, final approval of version
Samra Akram: Acquisition and interpretation of data
Amarah Ghani: Acquisition and analysis of data
Areeba Sohail: Interpretation of data
Annowish Nasir: Drafting the work

REFERENCES:

1. Unissa R, Monica B, Konakanchi S, Darak R, Keerthana SL, Kumar SA. Thalassemia: A Review. Asian Journal of Pharmaceutical Research 2018;8(3):195-202. DOI: 10.5958/2231-5691.2018.00034.5
2. Mettananda S, Pathiraja H, Peiris R, Wickramarathne N, Bandara D and de Silva U, et al. Blood transfusion therapy for â-thalassemia major and hemoglobin E â-thalassemia: Adequacy, trends, and determinants in Sri Lanka. Pediatric Blood & Cancer 2019;66(5):10. https://doi.org/10.1002/pbc.27643
3. Lal A, Wong TE, Andrews J, Balasa VV, Chung JH and Forester CM, et al. Transfusion practices and complications in thalassemia. Transfusion 2018; 58(12):2826-35. https://doi.org/10.1111/trf.14875
4. Shah FT, Sayani F, Trompeter S, Drasar E, Piga A. Challenges of blood transfusions in â-thalassemia. Blood reviews 2019 ;37. DOI: 10.1016/j.blre.2019.100588.
5. Bou-Fakhredin R, Tabbikha R, Daadaa H, Taher AT. Emerging therapies in â-thalassemia: toward a new era in management. Expert Opinion on Emerging Drugs. 2020 ;25(2):113-22. DOI: 10.1080/14728214.2020.1752180.
6. Ismail DK, El-Tagui MH, Hussein ZA, Eid MA, Aly SM. Evaluation of health-related quality of life and muscular strength in children with beta thalassemia major. Egypt J Med Hum Genet 2018. https://doi.org/10.1016/j.ejmhg.2018.04.005.
7. Ansari SH, Parveen S, Siddiqui S, Perveen K, Ahmed G, Kaleem B et al. Managing thalassemia in the developing world: an evidence-based approach for prevention, transfusion independency, and curative treatment with hematopoietic stem cell transplantation. Blood Adv. 2018;2(1):42-45 doi: 10.1182/bloodadvances.2018GS112057
8. Saleem N, Anwar A, Shahid N, Saleem R, Saleem Z, Asghar H et al. Perception of Parents of Thalassemic Child to Thalassemia in Pakistan. Cureus 2021; 13(8): e17615. doi:10.7759/cureus.17615
9. Yasmeen H, Hasnain S. Quality of Life of Pakistani Children with â-Thalassemia Major, Hemoglobin 2018; 42:5-6: 320-25. DOI: 10.1080/03630269.2018.1553183
10. Arian M, Mirmohammadkhani M, Ghorbani R, Soleimani M. Health-related quality of life (HRQoL) in beta-thalassemia major (â-TM) patients assessed by 36-item short form health survey (SF-36): a meta-analysis. Quality of Life Research. 2019; 28(2):321-34. DOI:10.1007/s11136-018-1986-1.
11. Kumar N, Turbitt E, Biesecker BB, Miller IM, Cham B and Smith KC et al. Managing the need to tell: Triggers and strategic disclosure of thalassemia major in Singapore. American Journal of Medical Genetics Part A. 2019; 179(5):762-9. https://doi.org/10.1002/ajmg.a.61107
12. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQLin pediatric cancer: reliability and validity of the pediatric quality of life inventory generic core scales, multidimensional fatigue scale, and cancer module. Cancer. 2002;94(7):2090–2106. doi: 10.1002/cncr.10428.
13. Greco F, Marino F. Social impact and quality of life of patients with â-Thalassemia: A systematic review. EMJ Hematol. 2022; DOI/10.33590/emjhematol/22-0004.
14. Ahmed S, Ayub M, Naeem M, Nazir FH, Hussain A, Ghilzai D et al. Thalassemia Patients from Baluchistan in Pakistan Are Infected with Multiple Hepatitis B or C Virus Strains. Am J Trop Med Hyg. 2021;104(4):1569-1576. doi: 10.4269/ajtmh.20-0740. PMID: 33534738; PMCID: PMC8045631.
15. Atmakusuma TD, Saragih EY, Rajabto W. Achievement of Pre-and Post-Transfusion Hemoglobin Levels in Adult Transfusion-Dependent Beta Thalassemia: Associated Factors and Relationship to Reduction of Spleen Enlargement. International Journal of General Medicine. 2021;14: 7515-21. DOI: 10.2147/IJGM.S338114
16. Tawarina I, Diba F. Emotional and Behavioral Aspects of Children with Thalassemia in Banda Aceh, Indonesia 2020;17(25):26-35. DOI: 10.5220/0008397202550260
17. Mahmoud MM, Helaly NM, Mohammed AA, Kamal MY. Quality Of Life of Children with Thalassemia in Alexandria. Alexandria Scientific Nursing Journal. 2019;21(1):69-80. DOI: 10.21608/asalexu.2019.206578

18. Mansoor S, Othman Z, Othman A, Husain M. A descriptive study on quality of life among adolescents with beta-thalassemia major in the Maldives. International Medical Journal. 2018;25(4):211-4. DOI:10.5281/zenodo.2588035

19. Zamanzadeh V, Valizadeh L, Ghahramanian A, Narenjbaghi SH. Personal social factors influential on the self-efficacy of the patients with thalassemia: A qualitative study. Journal of Nursing and Midwifery Sciences. 2021;8(2):120-7.DOI: 10.4103/JNMS.JNMS_124_20

20. Abdel Hakeem GL, Mousa SO, Moustafa AN, Mahgoob MH, Hassan EE. Health-related quality of life in pediatric and adolescent patients with transfusion dependent ß-thalassemia in upper Egypt (single center study). Health and Quality of Life Outcomes 2018; 16:59O

21. Ramprakash S, Raghuram CP, Marwah P, Soni R, Trivedi D and Khalid S et al. Splenomegaly May Increase the Risk of Rejection in Low-Risk Matched Related Donor Transplant for Thalassemia, This Risk Can Be Partially Overcome by Additional Immunosuppression during Conditioning. Biology of Blood and Marrow Transplantation. 2020;26(10):1886-93. Doi:org/10.1016/j.bbmt.2020.06.013

22. Tedone F, Lamendola P, Lopatriello S, Cafiero D, Piovani D and Forni G.L. Quality of Life and Burden of Disease in Italian Patients with Transfusion-Dependent Beta-Thalassemia. Journal of Clinical Medicine 2022; 11(1). DOI: 10.3390 /jcm11010015

23. Cappellini MD, Kattamis A, Viprakasit V, Sutcharitchan P, Pariseau J and Laadem A et al. Quality of life in patients with beta-thalassemia: a prospective study of transfusion-dependent and non-transfusion-dependent patients in Greece, Italy, Lebanon, and Thailand. Am J Hematol. 2019; 94(10): E261-E264. DOI: 10.1002/ajh.25584.

24. Az-zahra WF, Mardhiyah A, Nurhidayah I. The Depression Categories of Adolescent with Beta-Thalassemia Major. Journal of Nursing Care. 2019; 2(1). doi.org/10.24198/jnc. v2i1.20162

Original Article **Open Access**

Association of Myeloma in Patients of Chronic Kidney Disease; A Single Centered Study

Farzana Adnan Sheikh, Syed Tajammul Ali, Sidra Rashid, Mehwish Qamar, Khadijah Abid

ABSTRACT

Objective: To evaluate the frequency along with socio-demographic factors and clinical features of myeloma in patients with chronic kidney disease (CKD) presenting at a tertiary care hospital in Karachi, Pakistan.

Study design and setting: It was a cross-sectional study conducted at the Department of Nephrology and Hematology, Liaquat National Hospital, Karachi, Pakistan from Jan 2022 to Jul 2022.

Methodology: Patients of age>18 years of either gender having chronic kidney disease were included in the study. Detailed data regarding socio-demographic factors, clinical features and presence of multiple myeloma was obtained. Myeloma was diagnosed in the patients using WHO criteria i.e. presence of M-protein in urine or serum, presence of clonal plasma cells in bone marrow, and related tissue or organ failure. Data was entered and analyzed using SPSS version 25.

Results: The median age of the patients with chronic kidney disease was 54 years and most of them were males (63%). Myeloma was detected in only 14 patients with CKD. The proportion of myeloma was similar across chronic kidney disease stages, and statistically there was no significant association between chronic kidney disease stages and myeloma with p-value=0.08. There were no differences in hemoglobin, serum calcium, serum albumin, serum total protein, albumin/globulin (A/G) ratio, ESR, comorbid in patients with and without myeloma (p>0.05).

Conclusion: The frequency of myeloma among patients with chronic kidney disease was low.

Keywords: Chronic Kidney Disease, End Stage Renal Disease, Myeloma

How to cite this Article:
Sheikh FA, Ali ST, Rashid S, Qamar M, Abid K. Association of Myeloma in Patients of Chronic Kidney Disease; A Single Centered Study. J Bahria Uni Med Dental Coll. 2023;13(4):261-5 DOI: https://doi.org/10.51985 /JBUMDC2022123

INTRODUCTION:

Myeloma is a type of blood cancer characterized by abnormal plasma cells growth in the bone marrow.[1] Due to the fact that 90% of patients have multiple bone lesions at the time of presentation, it is frequently referred to as multiple myeloma.[2] Worldwide, myeloma accounts for 1% of all cancers and is the 2nd most frequent hematological malignancy.[3] Globally, the annual incidence of mylemo is 1.2 per 100,000 individuals and median age at the time of diagnosis is 70 years.[3] Approximately, 20% of myeloma patients have genetic abnormalitites and remaining 80% have chromosomal abnormalities.[4] In Asian population, an expeditious raised in the myeloma incidence is significant cause of great distrubance in the healthcare settings.[5]

Myeloma is more common in people of age more than 64 years, accounting for greater than 60% of incidences and 78% of deaths.[1] Furthermore, according to GLOBOCON 2020, the incidence of myeloma in Pakistan is 1.1% and 1.5% of deaths occurred due to it.[6] In recent years, the prognosis of myeloma has improved, from five year survival rate of 30% in 1990, when high-dose dexamethasone and melphalan were the only treatments to greater than 45% in 2006, with the advent of new agents and to greater than 50% in 2011.[1] Myeloma is found to be associated with various clinical manifestations like anemia, infection, renal impairment and bone, influencing mainly older age group and male gender.[1,3] There are various other environmental and genetic factors that have been suspected in the causes and pathogenesis of multiple myeloma, particularly radiation, pesticides, and chemicals such as asbestos, benzene, and arsenic.[5]

Kidney failure is one of the CRAB criteria i.e. anemia, renal

Farzana Adnan Sheikh
Assistant Professor, Department of Nephrology
Liaquat National Hospital and Medical College
Email: farzana12@gmail.com

Syed Tajammul Ali
Senior Registrar, Department of Nephrology
Liaquat National Hospital and Medical College
Email:syedatajammulali@yahoo.com

Sidra Rashid
Resident, Department of Nephrology
Liaquat National Hospital and Medical College
Email: sidra_mbbs@gmail.com

Mehwish Qamar
Senior Registrar, Department of Nephrology
Liaquat National Hospital and Medical College
Email: m_qamar@gmail.com

Khadijah Abid *(Corresponding Author)*
Lecturer, Department of Public Health
Shaheed Zulfikar Ali Bhutto Institute of Science and Technology
Email: khadijahadid@gmailcom

Received: 24-08-2022
Accepted: 02-10-2023

failure, hypercalcemia, and bone lesions that shows end organ damage. Kidney failure is one of the most frequent complications of myeloma, and it can influence different parts of kidney consisting the tubules, glomerulus, and interstitium.[4] In multiple myeloma patients, chronic kidney disease occurs mainly as a result of damage caused to renal tubules by FLCs (cast nephropathy). A variety of other nephrotoxic processes may also contribute to this damage including dehydration, hypercalcemia, nephrotoxic drugs, and infection.[7]

At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function (*estimated glomerular filtration rate* less than 60 mL/minute/1.73m^2), with 10 to 15% needing hemodialysis and approximately 1% progressing to end-stage kidney disease.[8,9] A Pakistani research also shows 35% of the myeloma patients had renal impairment (serum creatinine>2 mg/dl) at the time of diagnosis.[5] Studies by Mok et al. revealed that chronic kidney disease is positively associated with mortality among myeloma patients. Whereas, there was increased incidence of multiple myeloma in patients with reduced *estimated glomerular filtration rate* and dipstick proteinuria, the total multiple myeloma cases were 107 only, limiting conclusion of dose-response association and interactive effects of proteinuria and *estimated glomerular filtration rate*.[10,11] Literature has also revealed that improved survival of myeloma patients is linked with reversibility of renal dysfunction.[1,8,10,12] Treatment of myeloma with kidney disease includes removing aggravating factors of renal impairment, drinking enough water, alkalinizing urine, and preventing hypercalcemia as well as hyperuricemia. Dialysis is suitable for myeloma patients with severe renal function.[1,8,10,12]

Even after the advancement in therapeutic agents and supportive care, still the precise mechanisms for the development of myelomas in patients with kidney disease are incompletely understood. In Pakistan, limited data is available regarding the burden of myeloma in chronic kidney disease patients. Thus, in this study, we have evaluated the frequency and clinical features of myeloma along with socio-demographic factors of patients with chronic kidney disease presenting at a tertiary care hospital in Karachi, Pakistan.

METHODOLOGY:

It was a cross-sectional study conducted at the Department of Nephrology and Hematology, Liaquat National Hospital, Karachi, Pakistan for the duration of six months from Jan 2022 to Jul 2022. Sample size of 162 was estimated using frequency of renal impairment as 35%,[5] confidence limit as 7.4%, and level of significance as 5%. Patients of age>18 years of either gender having chronic kidney disease were included in the study. Chronic kidney disease was deemed as positive when patient had estimated glomerular filtration rate of less than 60 ml/minute/1.73m^2 for three months. Stages of chronic disease were labeled as stage 1: estimated glomerular filtration rate greater than 90ml.min/1.73m^2, stage 2: estimated glomerular filtration rate 60-89ml/min/1.73m^2, stage 3: estimated glomerular filtration rate 30-59ml/min/1.73m^2, stage 4: estimated glomerular filtration rate 15-29ml/min/1.73m^2 and stage 5: estimated glomerular filtration rate less than 15ml/min/1/73m^2 (or dialysis). Patients having hemoglobin less than 8 or more than 9 gm/dl, serum calcium level less than 9 mg/dl, anemia sensitive to erythropoietin stimulating agent, and established renal osteodystrophy were excluded from the study. Non-random consecutive sampling technique was applied for sample selection.

Ethical approval from ethical review committee of the Liaquat National Hospital was obtained (ERC# 0743-2022 LNH-ERC). Patients admitted in ward set up and ICU of nephrology department with chronic kidney disease were included. Prior to inclusion, patients were explained the rationale of study and written informed consent was taken from either patients or their families. Detailed data regarding socio-demographic factors (like age, gender), clinical features [like duration of end-stage renal disease (years), duration of hemodialysis, hemoglobin level, serum calcium, serum albumin level, serum total protein, albumin/globulin (A/G) ratio, *erythrocyte sedimentation rate (ESR)*, chronic kidney disease stages, serum immunofixation, serum protein electrophoresis], comorbids (like anemia, hypoalbuminemia, hypercalcemia, diabetes mellitus, hypertension, hyperparathyroidism, vitamin D intoxication] and presence of multiple myeloma was obtained. Myeloma was diagnosed in the patients using WHO criteria i.e. presence of M-protein in urine or serum, presence of clonal plasma cells in bone marrow, and related tissue or organ failure. All details were recorded by a principal investigator on a predesigned proforma having study variables. Exclusion criteria were followed strictly to avoid confounding variables.

Data was entered and analyzed using statistical packages for social sciences (SPSS) version 25. Normality of the numeric data was assessed using Shapiro-Wilk's test. Median and interquartile range were reported for numeric data like age, duration of end-stage renal disease (years), duration of hemodialysis, hemoglobin level, serum calcium, serum albumin level, serum total protein, albumin/globulin ratio, and *erythrocyte sedimentation rate (ESR)*, while frequencies and percentages were reported for categorical data like gender, anemia, hypoalbuminemia, hypercalcemia, anemia, diabetes mellitus, hypertension, hyperparathyroidism, vitamin D intoxication, chronic kidney disease stages, serum immunofixation, serum protein electrophoresis and myeloma. Comparison between chronic kidney disease stages and myeloma was done using Fisher exact test. Comparison between myeloma and socio-demographics, clinical features and comorbids were done using Mann-Whitney U test/Fisher exact test. The p-value less than and equal to 0.05 was considered statistically significant.

RESULTS:

Table 1 shows the baseline characteristics of patients with chronic kidney disease. The median age of the patients with chronic kidney disease was 54 years and most of them were males (63%). At the time of presentation, median hemoglobin was 8.3 g/dl, median serum calcium was 11 meq/l, median serum albumin was 2.6 mg/dl, median serum total protein was 8 mg/dl, median A/G ratio was 0.95 and median ESR was 87, respectively. All patients were anemic, whereas hypoalbuminemia (serum albumin in blood<3.5 gm/dl) was reported in 1.9%, and hypercalcemia (serum calcium>10.7 mg/dl) in 35.8 percent of patients. Almost 35.2% of the patients had stage 4 chronic kidney disease and 33.3% had stage 5 chronic kidney disease. Of 162 patients, 57.4% were diabetic, 42.6% were hypertensive and 22.2% were hyperparathyroidism, respectively.

Out of 162 patients, 51 patients had serum protein electrophoresis tested, of which 12 showed m spike in gamma region. Of 12 patients with M spike in gamma region, 6 had monoclonal and 6 had serum immunofixation. Myeloma was detected in only 14 patients with chronic kidney disease. Figure 1 shows that the proportion of myeloma was similar across chronic kidney disease stages, and statistically, there was no significant association between CKD stages and myeloma with p-value=0.08.

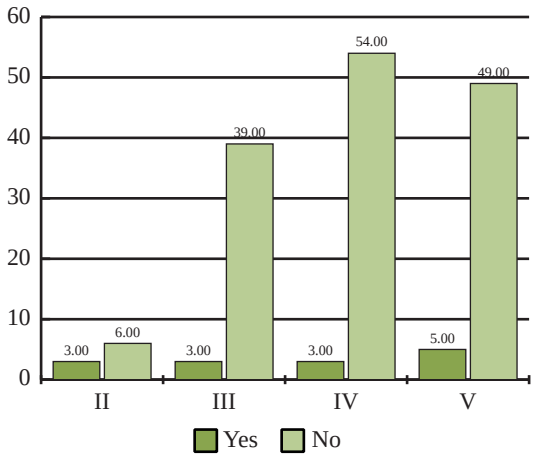
The median age of the chronic kidney disease patients with myeloma was 53.5 years and without myeloma was 54 years. There was no statistically significant relationship between age and myeloma with p-value=0.646. The majority of the patients with myeloma were males (8.8%) and 8.3% were females, however no statistically significant difference was observed between proportions of gender and myeloma with p-value=0.999. The median Hb was 8.45 g/dL of myeloma patients and 8.3 g/dL of without myeloma patients. The difference in Hb level was not statistically significant among patients with myeloma and without myeloma with p-value=0.816. The median serum calcium was 10.8 meq/l of myeloma patients and 11 meq/l of without myeloma patients. The difference in serum Ca level was not statistically significant among patients with myeloma and without myeloma with p-value=0.39. The median serum albumin levels were same for patients with and without myeloma (2.6 mg/dL) with p-value=0.944. The median total protein was same for patients with and without myeloma (8 mg/dL) with p-value=0.599. The median A/G ratio and ESR were also statistically similar between patients with and without myeloma with p-value=0.957 and 0.853. The most frequent comorbid among chronic kidney disease with myeloma was diabetes, followed by hypertension and hyperparathyroidism. There was no statistically significant difference observed in comorbids among patients with and without myeloma (p>0.05). (Table 2)

Table 1: Baseline characteristics of study sample (n=162)

Characteristics	
Age (years)	54 (45-64)
Gender	
Male	102 (63)
Female	60 (37)
Hb level (g/dl)	8.3 (8.0-8.9)
Serum Ca (meq/l)	11 (10.6-13.0)
Serum albumin levels (mg/dl)	2.6 (2.0-3.0)
Serum total protein (mg/dl)	8 (7-8)
A/G ratio	0.95 (0.8-1.0)
ESR	87 (66-100)
Comorbids	
Diabetes	93 (57.4)
Hypertension	69 (42.6)
Hyperparathyroidism	36 (22.2)
Chronic kidney disease stage	
II	9 (5.6)
III	42 (25.9)
IV	57 (35.2)
V	54 (33.3)

Data presented as Median (IQR) or n (%)

Figure 1: Comparison of myeloma and chronic kidney disease stages (n=162)



DISCUSSION:

Myeloma is a type of blood cancer and globally, the annual incidence of myeloma is 1.2 per 100,000 individuals. Due to the fact that 90% of patients have multiple bone lesions at the time of presentation, it is frequently referred to as multiple myeloma.[2] Worldwide, myeloma accounts for 1% of all cancers and is the 2nd most frequent hematological malignancy.[3] According to GLOBOCON 2020, the incidence of myeloma in Pakistan is 1.1% and 1.5% of deaths occurr due to it; kidney failure being one of the most frequent

Table 2: Comparison of socio-demographics, clinical features and comorbids among patients with and without myeloma (n=162)

Characteristics	Yes	No	p-value
Age (years)	53.5 (46-65)	54 (44-62)	0.646
Gender			
Male	9 (8.8)	93 (91.2)	0.999
Female	5 (8.3)	55 (91.7)	
Hb level (g/dl)	8.45 (8-8.5)	8.3 (8-8.9)	0.816
Serum Ca (meq/l)	10.8 (9.9-13)	11 (10.6-13)	0.39
Serum albumin levels (mg/dl)	2.6 (2-3)	2.6 (2-3)	0.944
Serum total protein (mg/dl)	8 (7-8)	8 (7-8)	0.599
A/G ratio	0.95 (0.8-1)	0.95 (0.8-1)	0.957
ESR	87.5 (67-110)	87 (66-100)	0.853
Comorbids			
Diabetes	7 (7.5)	86 (92.5)	0.583
Hypertension	6 (6.7)	83 (93.3)	0.406
Hyperparathyroidism	1 (2.8)	35 (97.2)	0.197

complications of myeloma.[4] Its management remains challenging. Cast nephropathy is the most common cause of severe kidney dysfunction in multiple myeloma.[7] At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function.[8,9,13] Shaheen et al. also revealed that 35% of the myeloma patients had renal impairment (serum creatinine>2 mg/dl) at the time of diagnosis.[5] Even after the advancement in treatment options, still the precise mechanisms for the development of myeloma in patients with kidney disease is incompletely understood.[3,14-18] Hence, in the current study, we have evaluated the frequency and clinical features of myeloma along with socio-demographic factors among patients with chronic kidney disease.

Globally, median age at the time of diagnosis is 70 years.[3] In the current study, myeloma was diagnosed in 14 patients with chronic kidney disease. Among them, 8 cases had stage 4-5 chronic kidney disease. We found the median age of our patients with myeloma was 53.5 years. In other studies, by Soleymanian et al. and Kyle et al., myeloma was frequently present among patients of older age and median age at the time of diagnosis was 59-66 years.[19,20] While, Ludwig et al. found median age at the time of diagnosis as 70 years.[21] In another similar Indian study by Devi et al., the mean age of myeloma patients was 58.8 years.[22] Moreover, we found proportion of myeloma was higher among males than females, which is similar to the previous studies by Soleymanian et al. and Shaheen et al.[19,23] Basharat et al. also reported most of the patients with myeloma were males (73%).[5]

The most frequent comorbid in our patients with myeloma and chronic kidney disease was diabetes. Hence, the patients with chronic kidney disease had higher risk of myeloma if they were diabetic. At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function (*estimated glomerular filtration rate* less than 60 mL/minute/1.73m^2), with 10 to 15% needing hemodialysis and approximately 1% progressing to end-stage kidney disease.[8,9] In the current study, all the patients with myeloma were anemic with median hemoglobin level as 8.45 gm/dl, which contributes mainly to fatigue and weakness. Whereas, in other studies, the frequency of anemia was reported as 73 to 88%.[19,20] Basharat et al. found that 93% of the myeloma patients had anemia. Kaur et al. also found that 88% of the patients with multiple myeloma had hemoglobin level less than 12 mg/dl.[24] Kyle et al. showed that 73% of the myeloma patients had normocytic normochromic anemia at presentation.[20] In patients with myeloma, anemia can be analogous to kidney dysfunction, bone marrow replacement or can be due to dilution in the case of huge M-protein. Therefore, it was anticipated that kidney failure in myeloma patients with chronic kidney disease would frequently be caused by hypercalcemia, which is also a common consequence of anemia.[19] In our study, we also found patients with myeloma and chronic kidney disease had lower level of serum calcium. According to Kyle et al. 28% of the myeloma patients had hypercalcemia.[20] Monoclonal protein binding with calcium may be because of increase in serum calcium.[5]

Despite efforts to control confounding factors, there are a number of limitations in the present study. The sample size of the study was small and it was a single center study. Therefore, findings cannot be generalized to entire population. The design of the study was cross-sectional that's why we were unable to identify the cause-effect relationship between myeloma, chronic kidney disease and comorbids. In future, prospective studies with larger sample sizes should be done in order to increase the generalizability of findings.

CONCLUSION:

Frequency of myeloma among patients with chronic kidney disease was low. Hence, renal impairment in patients with multiple myeloma is a common complication that worsen the prognosis of the disease. Treating early and effectively with new chemotherapy drugs can stop or delay the progression of disease and improve survival outcomes

Authors Contribution:
Farzana Rashid: Conception, design, literature review, critical review, Final approval of manuscript
Syed Tajammul Ali: Conception, design, literature review, critical review, Final approval of manuscript
Sidra Rashid: Methodology, discussion, Final approval of manuscript
Mehwish Qamar: Interpretation of results, critical review, Final approval of manuscript
Khadijah Abid: Data analysis and drafting of manuscript, Final approval of manuscript

REFERENCES:

1. Li S, Gong T, Kou C, Fu A, Bolanos R, Liu J. Clinical Outcomes Associated With Chronic Kidney Disease in Elderly Medicare Patients With Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2021;21(6):401-12.e24.'10.1016/j.clml.2021.01.015:'10.1016/j.clml.2021.01.015.

2. Understanding Myeloma, Cancer Council Australia ©2018. Last medical review of source booklet: September 2018. .
3. Shi H, Chen Z, Xie J, Chen N. The Prevalence and Management of Multiple Myeloma-Induced Kidney Disease in China. Kidney Dis (Basel). 2016;1(4):235-40.'10.1159/000443492:'10.1159/000443492.
4. Vakiti A, Padala SA, Mewawalla P. Myeloma Kidney. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499952/.
5. Basharat S, Batool Z, Ali N. Clinical profile of multiple myeloma in a tertiary care hospital of Peshawar, Pakistan. Khyber Med Univ J 2019;11(3):152-5. DOI: 10.35845/ KMUJ. 2019.18790.
6. WHO. GLOBOCAN 2020: International Agency for Research on Cancer; 2021 [Available from: https://gco.iarc.fr/today/data/factsheets/populations/586-pakistan-fact-sheets.pdf.
7. Katagiri D, Noiri E, Hinoshita F. Multiple myeloma and kidney disease. ScientificWorldJournal. 2013;2013:487285.'10.1155/2013/487285:'10.1155/2013/487285.
8. Owoyemi I, Sethi S, Leung N. Kidney Injury in Multiple Myeloma: A Kidney Biopsy Teaching Case. Kidney Medicine. 2021;3(2):303-6.'https://doi.org/10.1016/ j.xkme.2020.10.013:'https://doi.org/10.1016/j.xkme.2020.10.013.
9. Rana R, Cockwell P, Drayson M, Cook M, Pratt G, Cairns DA, et al. Renal outcome in patients with newly diagnosed multiple myeloma: results from the UK NCRI Myeloma XI trial. Blood Adv. 2020;4(22):5836-45.'10.1182/bloodadvances.2020002872:'10.1182/bloodadvances.2020002872.
10. Mok Y, Matsushita K, Ballew SH, Sang Y, Jung KJ, Lee S, et al. Kidney Function, Proteinuria, and Cancer Incidence: The Korean Heart Study. Am J Kidney Dis. 2017;70(4):512-21.'10.1053/j.ajkd.2017.03.018:'10.1053/j.ajkd.2017.03.018.
11. Mok Y, Matsushita K, Sang Y, Ballew SH, Grams M, Shin SY, et al. Association of Kidney Disease Measures with Cause-Specific Mortality: The Korean Heart Study. PLoS One. 2016;11(4):e0153429.'10.1371/journal.pone.0153429:'10.1371/journal.pone.0153429.
12. Mian HS, Fiala MA, Sanchez L, Vij R, Wildes TM. Renal failure among multiple myeloma patients utilizing carfilzomib and associated factors in the "real world". Ann Hematol. 2021;100(5):1261-6.'10.1007/s00277-021-04420-3:'10.1007/s00277-021-04420-3.
13. Sharma R, Jain A, Jandial A, Lad D, Khadwal A, Prakash G, et al. Lack of Renal Recovery Predicts Poor Survival in Patients of Multiple Myeloma With Renal Impairment. Clinical Lymphoma Myeloma and Leukemia. 2022;22(8):626-34.'https://doi.org/10.1016/j.clml.2022.04.013:'https://doi.org/10.1016/j.clml.2022.04.013.
14. Rosner MH, Jhaveri KD, McMahon BA, Perazella MA. Onconephrology: The intersections between the kidney and cancer. CA: A Cancer Journal for Clinicians. 2021;71(1):47-77.'https://doi.org/10.3322/caac.21636:'https://doi.org/10.3322/caac.21636.
15. Gulla A, Anderson KC. Multiple myeloma: the (r)evolution of current therapy and a glance into future. Haematologica. 2020;105(10):2358-67.'10.3324/haematol. 2020.247015 :'10.3324/haematol.2020.247015.
16. Dima D, Jiang D, Singh DJ, Hasipek M, Shah HS, Ullah F, et al. Multiple Myeloma Therapy: Emerging Trends and Challenges. Cancers (Basel). 2022;14(17).'10.3390/cancers14174082 :'10.3390/cancers14174082.
17. Rodriguez-Otero P, Paiva B, San-Miguel JF. Roadmap to cure multiple myeloma. Cancer Treat Rev. 2021;100:102284.'10.1016/j.ctrv.2021.102284:'10.1016/j.ctrv.2021.102284.
18. Kint N, Vlayen S, Delforge M. The treatment of multiple myeloma in an era of precision medicine. Expert Review of Precision Medicine and Drug Development. 2019;4(3):153-62.
19. Soleymanian T, Soleimani A, Musavi A, Mojtahedi K, Hamid G. Outcome of patients with multiple myeloma and renal failure on novel regimens. Saudi Journal of Kidney Diseases and Transplantation. 2016;27(2):335-40.'10.4103/1319-2442.178557:'10.4103/1319-2442.178557.
20. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33.'10.4065/78.1.21:'10.4065/78.1.21.
21. Ludwig H, Miguel JS, Dimopoulos MA, Palumbo A, Garcia Sanz R, Powles R, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014;28(5):981-92.'10.1038/leu.2013. 293:'10. 1038/ leu.2013.293.
22. Devi A, Sharma T, Singh Y, Sonia H. Clinicopathological profile of patients with non-hodgkin's lymphoma at a regional cancer center in Northeast India. Journal of the Scientific Society. 2017;44(3):140-4.'10.4103/jss.JSS_42_17 :'10.4103/jss.JSS_42_17.
23. Shaheen H, Ghanghroo I, Malik I. Clinicopathological features and management of Pakistani patients with multiple myeloma. J Pak Med Assoc. 1999;49(10):233-7.
24. Kaur P, Shah BS, Baja P. Multiple myeloma: a clinical and pathological profile. Gulf J Oncolog. 2014;1(16):14-20.

Original Article **Open Access**

Weight Reducing Effect of Moringa Oleifera Leaves Against Induced Obesity in Rabbits

Syed Saqib Khalid, Tabassum Zehra, Fizzah Ali, Fizza Batool

ABSTRACT

Objectives: To study the weight-reducing effect of M. Oleifera Leaves against induced obesity in rabbits.

Study Design and Settings: It was an animal study conducted in the Department of Pharmacology, Liaquat National Hospital & Medical College, Karachi.

Methodology: The study period was 6 months, and random sampling was done. Twenty four Healthy rabbits of either sex, weighing 1–2 kg and aged 1-3 years, were included in the study. Sick rabbits weighing less than 1 kg or more than 2 kg and aged less than 1 year or more than 3 years were excluded from the study.

Results: The weight of Group B animals fed with a high-fat diet (HFD) for 28 days increased significantly from 1.28±0.07 to 1.88 ± 0.17. While the weight of Group C and D rabbits which were fed with M. oleifera extract(300mg/kg and 600mg/kg) along with a HFD for 28 days, increased slightly from 1.38±0.07 to 1.53± 0.08 and from 1.25±0.13 to 1.38± 0.14 respectively. P-value of weight on Day 28 also became significant with a P-value of (0.000), which was (0.176) on Day 0, proving the anti-obesity effects of M. oleifera leaves.

Conclusion: In our study, we found out that there was a significant weight-reducing effect of M. oleifera leaves against obesity induced rabbits as well as skin fold thickness was also decreased. This study also indicates that the given dose of M. oleifera leaves extracts are devoid of any side effects.

Keywords: Body mass index, High-fat diet, Moringa oleifera, Obesity, World Health Organization

How to cite this Article:
Khalid SS, Zehra T, Ali F, Batool F. Weight Reducing Effect of Moringa Oleifera Leaves Against Induced Obesity in Rabbits. J Bahria Uni Med Dental Coll. 2023;13(4):266-70 DOI: https://doi.org/10.51985 /JBUMDC2022143

INTRODUCTION:

Today, obesity has become a serious health concern and a possible risk for many diseases worldwide. World Health Organization (WHO) defined obesity as having a body mass index of 30 kg/m2 or more. A Body Mass Index over the normal range of 18 to 25 kg/m^2 is typical in Western societies. It has been connected to inactive lifestyles and Western food intake (rich in saturated fat and calories).[1]

The National Heart, Lung, and Blood Institute's "Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline" states that moderate-intensity exercise combined with suitable lifestyle and dietary adjustments should be the preferred method of weight loss treatment. However, epidemiological and clinical research has demonstrated how difficult it is to sustain a long-term healthier lifestyle. Therefore, much research has been done on natural supplement items that primarily aid people in their fight against obesity.[2]

Reports indicate that the biological activity of M. oleifera includes prevention of gastric ulcers, reducing blood glucose levels, decreasing blood pressure, and anti-inflammatory qualities. Moringa oleifera leaves protect against a wide range of potentially dangerous illnesses, including bacterial growth, cancer, oxidative stress, inflammation, hepatic fibrosis, liver damage, and hypercholesterolemia. It has also been shown to improve regulation of hormones in the kidneys, liver, and thyroid.[3]

Moringa oleifera also have beneficial effects on brain as one study shows that it can protect male wistar rats against ketamine-induced memory problems, and NMDA receptors may play a role in this protective action of M. oleifera.[4]

Research also shows that mice performed better during reproduction when they consumed Moringa oleifera leaves. Dietary Moringaoleifera leaves lowered serum

Syed Saqib Khalid *(Corresponding Author)*
Lecturer, Department of Pharmacology
Liaquat National Hospital and Medical College, Karachi
Email: saqibkhalid32@gmail.com

Tabassum Zehra
Professor & HOD, Department of Pharmacology,
Liaquat National Hospital and Medical College, Karachi
Email: drtabassum.zehra@lnh.edu.pk

Fizzah Ali
Assistant Professor, Department of Pharmacology,
Liaquat National Hospital and Medical College, Karachi
Email: dr.fizzah.ali@lnh.edu.pk

Fizza Batool
Lecturer, Department of Pharmacology,
Liaquat National Hospital and Medical College, Karachi
Email: fizza.batool@lnh.edu.pk

Received: 03-11-2022
Accepted: 12-09-2023

Malondialdehyde, but more significantly, decreased the frequency of defective sperm.[5]

In mice, the polysaccharide from Moringaoleifera leaves has been shown to modulate the intestinal microbial composition by increasing the abundance of bacteria linked to weight reducing effects, short chain fatty acid generation, and lactic acid production. These results suggest that the polysaccharide found in M. oleifera leaves may be a useful prebiotic with health-enhancing properties.[6]

M. oleifera also has garnered significant attention as a chemotherapeutic approach due to possible anti-inflammatory and antioxidant properties, and higher flavonoid content compared to other vegetables and fruits.[7]

The major metabolic enzymes that are linked to obesity are pancreatic lipase, α-amylase, and α-glucosidase, which were strongly suppressed by M. oleifera leaves. Therefore, M. oleifera leaves may be considered a readily available health supplement source for reducing obesity.[8]

This study outlined an anti-obesity function of M. oleifera leaves powder in experimentally induced obesity in rabbits, a species that has recently been studied for hypocholesterolemic action of M. oleifera.

The purpose of this study was to determine whether M. oleifera leaf had any therapeutic value for treating obesity in rabbits.

Some pharmacological drugs are used to treat obesity, but each drug has their undesirable side effects and slow onset of action, and some are expensive. If the weight-reducing effects of M. Oleifera leaves are established, they can replace the pharmacological drugs for treating obesity.

METHODOLOGY:

It was an animal study performed in the Department of Pharmacology along with Animal House, Liaquat National Hospital & Medical College, Karachi. The study duration was six months from 1st January 2022 to 30th June 2022 after approval from the research and ethical committee. Ethical permission for the current study was taken by the Ethical Review Committee of Liaquat National Hospital & Medical College, Karachi. (Ref: App # 0658-2021 LNH – ERC). Data that were obtained during the study was kept extremely confidential.

Sample size was 24 Rabbits. Sample size was calculated by using below formula.

Minimum numbers of animals per group:

Minimum n = 10/k + 1

n = number of subjects per group and k = number of groups

n = 10/4 + 1

n = 2.5 + 1 = 3.5

Total Minimum numbers of animals required:

Minimum N = Minimum n x k

Minimum N = 3.5 x 4= 14

Random sampling was done and 24 Healthy rabbits of either sex, Weighing 1 – 2 kg and Aged 1 - 3 years, were included in the study. Sick Rabbits Weighing less than 1 kg or more than 2 kg and aged less than one year or more than three years were excluded from the study. Rabbits were divided into groups A, B, C, and D, with six animals in each group.

Group A: represent the standard control in which the rabbits were given a regular diet and free access to water for 28 days.

Group B: represent a negative control in which the rabbits were given a high-fat diet for 28 days.

Group C: represent a test treatment in which rabbits were given M. oleifera extract(300mg/kg) along with a high-fat diet for 28 days.

Group D: represents test treatment in which rabbits were given M.oleifera extract (600mg/kg) along with a high-fat diet for 28 days.[10]

Previous reports of an acute toxicity investigation using a single dosage of orally given 2 g/kg extracts of M. oleifera(leaf) indicate that these concentrations which are used in our study are safe to use.

The body weight, skin fold thickness, and body temperature were recorded on day 0 and then weekly consecutively for 28 days.

Fine powder of M. oleifera leaves (Stock Number: 124876300_PK-1282732171) was brought from Moringa Powder Store Pakistan and stored in a clean, sterile glass container. 300mg and 600 mg of M. oleifera leaf powder/rabbit/day were administered with a high-fat diet according to the experimental design.

Rabbits that were fed with a regular diet include hay which was brought from the local market on an everyday basis.

High-fat diet induced obesity in rabbits is considered a reliable tool for evaluating anti-obesity activity. A high-fat diet includes 10% fat (2/3 corn oil and 1/3 coconut oil) added to the regular rabbit diet.

Statistical analysis: Data was analyzed on SPSS version 22.0 (IBM, incorporation, USA). The results were expressed as means ± standard deviation. One way ANOVA test is applied. Statistical significance was taken at $P<0.05$.

RESULTS:

Body weight, skin fold thickness and temperature of animals, of all groups were analyzed and compared on Day 0, 7, 14, 21 and 28.

The weight of Group B animals fed with a high fat diet for 28 days increased significantly from 1.28±0.07 to 1.88 ± 0.17. While the weight of Group C and D rabbits which were fed with M. oleifera extract(300mg/kg and 600mg/kg) along with a HFD for 28 days, increased slightly from

1.38±0.07 to 1.53± 0.08 and from 1.25±0.13 to 1.38± 0.14 respectively. P-value of Weight on Day 28 also became significant with a P-value of (0.000), which was (0.176) on Day 0, proving the anti-obesity effects of M. oleifera leaves.

Skin fold thickness also increased significantly from 1.08±0.07 to 1.45 ±0.20 in Group B animals fed with a HFD for 28 days. There was only a slight increase in Skin fold thickness from 1.16±0.10 to 1.23± 0.10 and from 1.16±0.08 to 1.25± 0.08, respectively, in Group C and D animals fed with M. oleifera extract(300mg/kg and 600mg/kg) along with HFD for 28 days. The P-value of Skin fold thickness on Day 28 was close to significant with a P-value of (0.061), which was (0.411) on Day 0.

There was a noteworthy drop in Body temperature from 39.08±0.33 to 37.18± 0.22 in Group B animals fed with a HFD for 28 days, while there was a rise in Body temperature from 38.41±0.16 to 39.18.± 0.17 and from 38.63±0.31 to 39.28± 0.09 in Group C and Group D animals fed with M. oleifera extract(300mg/kg and 600mg/kg) along with a HFD for 28 days. P-value of Body temperature on Day 28 also became significant with a P-value of (0.000), which was (0.006) on Day 0, indicating that intake of M. Oleifera leaves can increase body temperature slightly.

DISCUSSION:

Obesity has been declared a worldwide epidemic by WHO.[13] It has become a serious health concern and a possible risk for many diseases worldwide. When a person's amount of fat tissue increases to the point that it negatively impacts their mental and physical well-being and shortens their life span, they are said to be obese. Recent studies showed that interaction of genetic, environmental, psycho-behavioral, hormonal, metabolic, cultural, and socioeconomic elements might contribute to the development of obesity. The incidence of the world's main severe illnesses and primary causes of death is dramatically increased by obesity. Severe obesity is often associated to a number of other serious medical conditions. These include high cholesterol, high blood pressure, diabetes type II, gallstones, fatty liver disease, pulmonary hypertension, sleep apnea, and even certain forms of cancer.[14]

A study of the available literature reveals that several different herbal plants are used in the treatment of obesity. These include fucus vesiculosus, citrus aurantium, yacon syrup, curcumin, nigella sativa, camellia synensis, green tea, and black Chinese tea.[1]

Vitamins, phenolic acids, flavonoids, isothiocyanates, tannins, and saponins are some of the many bioactive components found in substantial concentrations throughout different M. oliefera plant parts. They've all been researched for their health benefits.[15]

This study outlined an anti-obesity function of M. oleifera leaves powder in experimentally induced obesity in rabbits, a species that has recently been studied for hypocholesterolemic action of M. oleifera.

Study conducted by (Nahar et al., 2016) revealed that Body weight, thoracic (TC) and abdominal (AC) circumferences, and body mass index, all increased significantly in rats fed a high-fat diet. A comparable research found that HFD animals gained much more weight than pellet-fed animals (Bais, Singh, & Sharma, 2014). Our findings, in which Group B animals given an HFD for 28 days had their weight grow dramatically from 1.280.07 to 1.880.17 kgs, are supported by these investigations.

Research from (Nahar et al., 2016) also found that both single-dose and repeated-dose administrations of M. oleifera leaf powder successfully decreased body mass index (BMI) in obese participants which is in accordance with our study in which Groups C and D treated with M. oleifera leaves

Table 1: Mean differences among different group with respect to weight, skin fold thickness and body temperature

Parameters		Group A	Group B	Group C	Group D	P-value
Weight	Day 0	1.28±0.11	1.28±0.07	1.25±0.13	1.25±0.13	0.176
	Day 7	1.33±0.15	1.38±0.13	1.28±0.11	1.28±0.11	0.496
	Day 14	1.38±0.13	1.45±0.13	1.31±0.11	1.31±0.11	0.150
	Day 21	1.38± 0.13	1.65±0.19	1.33±0.15	1.33±0.15	0.006
	Day 28	1.45±0.13	1.88± 0.17	1.38±0.14	1.38±0.14	0.000
Skin fold thickness	Day 0	1.18±0.16	1.08±0.07	1.16±0.08	1.16±0.08	0.411
	Day 7	1.21±0.11	1.20±0.08	1.23±0.10	1.23±0.10	0.927
	Day 14	1.25±0.12	1.28±0.11	1.26±0.08	1.26±0.08	0.363
	Day 21	1.26±0.12	1.31±0.17	1.28±0.07	1.28±0.07	0.564
	Day 28	1.28±0.14	1.45±0.20	1.25±0.08	1.25±0.08	0.061
Body temperature	Day 0	38.78±0.31	39.08±0.33	38.63±0.31	38.63±0.31	0.006
	Day 7	39.13±0.20	39.46±0.45	38.90±0.24	38.90±0.24	0.02
	Day 14	39.16±0.26	38.96±0.67	39.10±0.15	39.10±0.15	0.437
	Day 21	38.90±0.46	38.06±0.16	39.03±0.08	39.03±0.08	0.000
	Day 28	38.86±0.43	37.18±0.22	39.28±0.09	39.28±0.09	0.000

extract at 300 and 600mg dosages, respectively, had only a modest rise in weight in comparison to an obese control group in which the weight increase was highly significant.

Additionally a similar study reported that the use of a HFD result in a considerablerise in body weight. The percentage of gain in weight of body of rats fed with the HFD supplemented with extract of M. oleifera leaves was notably lesser than that in the HFD group, which coincides with our study in which P-value of Weight at Day 28 becomes significant (0.000) which was (0.176) at Day 0 proving anti-obesity effects of M. oleifera leaves.[16]

The study performed by Irfan et al., 2016 evaluated that the diabetic rats fed with M. oleifera leaf extract produced an utmost loss in body weight on the 7th day of study. Moreover, body weight loss at the completion of oral doses was progressively declining, which supports our study.[17]

Another study conducted by Madkhali H et al., 2019 revealed when HFD was given to animals, it resulted in a considerable rise in body weight. On the other hand, body weight was considerably decreased in HFD-induced obese rats that were given M. oleifera leaves extract in a dose-dependent manner, which is in accordance with our study.[18]

The study conducted by Othman A et al., 2019 support our study and provides evidence that HFD rats demonstrate a marked rise in weight of body compared to animals given normal diet, and two weeks of M. oleifera extract therapy noticeably decreases weight of body compared to HFD supplemented rats.[10]

Kilany O et al., 2020 observed that administration of M. oleifera seed oil extract to rats significantly decreased body weight; in contrast, in our study, M. oleifera leaves extracts were used instead of M. oleifera seed oil.[19]

The HFD group showed statistically significant weight gain in a research by Dhungel et al., 2009. According to their findings, those who followed the HFD gained about 24% more weight than those who followed the Low Fat Diet, and those on the High Fat Diet also had increases in skinfold thickness (SFT) in the fourth and tenth weeks of the research. Consistent with these findings, we found that skin fold thickness increased significantly from 1.08 ±0.07 to 1.45 ±0.20 in Group B animals given the high-fat diet.

Research done by Bais S et al., 2014found that rats getting a HFD showed a significant decrease in rectal body temperature observed on Day 49 while giving M. oleifera extract (200 and 400mg/kg) dose-dependently increased the body temperature. Our study is in accordance with this study, and there was a considerable drop in Body temperature from 39.08±0.33 to 37.18± 0.22 in Group B animals fed with a HFD while there was a rise in Body temperature from 38.41±0.16 to 39.18.± 0.17 and 38.63±0.31 to 39.28± 0.09 in Group C and Group D animals, respectively, fed with M. oleifera extract(300mg/kg and 600mg/kg).[20]

Further, studies are carried out to determine the active principle of this plant, followed by the identification of the mechanistic approach of M. oleifera leaf powder that helps in weight management.

CONCLUSION:

Many pharmaceutical methods have been explored for treating obesity, but only a few are safe, and the majority have undesirable side effects. The search for plant-based anti-obesity medications is, therefore, an option. Based on our findings, M. oleifera leaves significantly reduced body weight and skin fold thickness in obese rabbits. This research also shows that the recommended dose of M. oleifera leaves extract is safe and without side effects.

Authors Contribution:
Syed Saqib Khalid: developed the protocol of study and carried out data collection.
Tabassum Zehra: conducted literature review.
Fizzah Ali: assisted in data collection.
Fizza Batool: contributed in statistical analysis.

REFERENCES:

1. Nahar S, Faisal F, Iqbal J, Rahman M, Yusuf DMA. Antiobesity activity of Moringa oleifera leaves against high fat diet-induced obesity in rats. International Journal of Basic and Clinical Pharmacology. 2016:1263-8. DOI: https://doi.org/10.18203/2319-2003.ijbcp20162427
2. Aziza S, Elsenosi Y, Ghada H, El S, Hussein S. Moringa Oleifera improve lipid metabolic disorders in obesity induced oxidative stress in rats. Benha Veterinary Medical Journal. 2019;35. https://doi.org/10.21608/BVMJ.2018.96443
3. Vergara-Jimenez M, Almatrafi MM, Fernandez ML. Bioactive Components in Moringa Oleifera Leaves Protect against Chronic Disease. Antioxidants (Basel, Switzerland). 2017;6(4). doi: 10.3390/antiox6040091
4. Afrin S, Hossain A, Begum S. Effects of Moringa oleifera on working memory: an experimental study with memory-impaired Wistar rats tested in radial arm maze. BMC Research Notes. 2022;15(1):314. DOI: 10.1186/s13104-022-06219-5
5. Zeng B, Luo J, Wang P, Yang L, Chen T, Sun J, et al. The beneficial effects of Moringa oleifera leaf on reproductive performance in mice. Food Science & Nutrition. 2019;7(2):738-46. doi: 10.1002/fsn3.918
6. The Beneficial Effects of a Polysaccharide from Moringa oleifera Leaf on Gut Microecology in Mice. Journal of Medicinal Food. 2019;22(9):907-18. DOI: 10.1089/jmf .2018.4382
7. Lin M, Zhang J, Chen X. Bioactive flavonoids in Moringa oleifera and their health-promoting properties. Journal of Functional Foods. 2018;47:469-79. https://doi.org/10.1016/j.jff.2018.06.011
8. Swamy GM, Meriga B. Therapeutic effect of Moringa oleifera leaf extract s on oxidative stress and key metabolic enzymes related to obesity. Internationa l Journal of Pharmaceutical Sciences and Research. 2020;11(4):1949-57. DOI: 10.13040/IJPSR.0975-8232.11(4).1949-57
9. Arifin WN, Zahiruddin WM. Sample Size Calculation in Animal Studies Using Resource Equation Approach. The Malaysian journal of medical sciences : MJMS. 2017;24(5):101-5. DOI: 10.21315/mjms2017.24.5.11

10. Othman A, Amer M, Basos A, El-Missiry MA. Moringa oleifera leaf extract ameliorated high-fat diet-induced obesity, oxidative stress and disrupted metabolic hormones. Clinical Phytoscience. 2019;5. DOI https://doi.org/10.1186/s40816-019-0140-0

11. Jacob J, Amalraj A, Divya C, Janadri S, Manjunatha PM, Gopi S. Oral toxicity study of sports nutritional powder in Wistar rats: A 90 day repeated dose study. Toxicology reports. 2018;5:497-503. https://doi.org/10.1016/j.toxrep.2018.04.001

12. Dhungel S, Sinha R, Sinha M, Paudel BH, Bhattacharya N, Mandal M. High fat diet induces obesity in British Angora Rabbit: A model for experimental obesity. Indian journal of physiology and pharmacology. 2009;53:55-60.

13. El-Shehawi AM, Alkafafy M, El-Shazly S, Sayed S, Farouk S, Alotaibi S, et al. Moringa oleifera leaves ethanolic extract ameliorates high fat diet-induced obesity in rats. Journal of King Saud University-Science. 2021;33(6):101552. DOI https://doi.org/10.1186/s40816-019-0140-0

14. Ahmed H, Metwally F, Rashad H, Zaazaa A, Ezzat S, Salama M. Moringa oleifera offers a multi-mechanistic approach for management of obesity in rats. 2014;29:98-106.

15. Vergara-Jimenez M, Almatrafi MM, Fernandez ML. Bioactive Components in Moringa Oleifera Leaves Protect against Chronic Disease. Antioxidants. 2017;6(4):91. DOI: 10.3390/antiox6040091

16. Mabrouki L, Rjeibi I, Taleb J, Zourgui L. Cardiac Ameliorative Effect of Moringa oleifera Leaf Extract in High-Fat Diet-Induced Obesity in Rat Model. BioMed Research International. 2020;2020:1-10. DOI: 10.1155/2020/6583603

17. Irfan H, Abdullah M, Khan N, Sadikun A. Effect of Ethanolic Extract of Moringa oleifera Lam. Leaves on Body Weight and Hyperglycemia of Diabetic Rats. Pakistan Journal of Nutrition. 2016;15:112-7. DOI: 10.3923/pjn.2016.112.117

18. Madkhali H, Alharthy M, Asiri M, Ganaie M, Ansari M, Rehman NU, et al. Moringa oleifera Lam. (family Moringaceae) leaf extract attenuates high-fat diet-induced dyslipidemia and vascular endothelium dysfunction in Wistar albino rats. 2019;18:2597-604. DOI: 10.4314/tjpr.v18i12.20

19. Kilany O, Abdelrazek H, Aldayel T, Abdo S, M.A.Mahmoud M. Anti-obesity potential of Moringa olifera seed extract and lycopene on high fat diet induced obesity in male Sprauge Dawely rats. Saudi Journal of Biological Sciences. 2020;27. https://doi.org/10.1016/j.sjbs.2020.06.026

20. Bais S, Singh G, Sharma R. Antiobesity and Hypolipidemic Activity of Moringa oleifera Leaves against High Fat Diet-Induced Obesity in Rats. Advances in Biology. 2014;2014:1-9. https://doi.org/10.1155/2014/162914

Original Article **Open Access**

Impact of Maternal Body Mass Index (BMI) and Age on Pregnancy Outcomes at a Tertiary Care Hospital

Shazia Iffet, Ayesha Arif, Sadaf Moin, Aisha Raja, Sadia Arif, Nadia Arif

ABSTRACT

Objectives: To analyze the role of maternal BMI and age on pregnancy outcomes.

Study design and Setting: A retrospective cohort study CMH, Abbottabad from 1st August 2022 to 31st January 2023

Methodology: A retrospective cohort study was done over a period of 6 months in 500 post-natal women whose BMI were calculated and recorded at first trimester during their booking visit and eventually delivered at combined military hospital, Abbottabad. Data related to age, BMI, gestational age at the time of delivery, spontaneous or induction of labour and mode of delivery were evaluated.

Results: The study included 500 female patients. The mean age and BMI were 32±11.5 years and 28.8±8 respectively. 140 (28%) females had normal weight, 310(62%) and 50(10%) were overweight and obese respectively. The variable age at the time of booking was divided into three groups = 20 years, 21-35 years, and 36-42 years which included 80(16.4%), 275(55%) and 145(29%) patients respectively. Multigravida were 285(57%) and prim gravida were 215(43%). Induction was given to 275(55%) and those who went into spontaneous labour were 225(45%). Delivery at term that is = 37 weeks was 455(91%) and only 45(9%) were delivered before 37 weeks. Percentage of women having a spontaneous vaginal delivery was 230(46%) and 250(50%) had LSCS and 20(4%) underwent instrumental delivery.

Conclusion: It was evident that raised BMI and maternal age had confounding effects on pregnancy outcomes. The incidence of LSCS was more in patients with higher BMI and age.

Keywords: Body Mass Index (BMI), obesity, gestational age, Lower-Segment Cesarean Section (LSCS).

How to cite this Article:
Iffet S, Arif A, Moin S, Raja A, Arif S, Arif N. Impact of Maternal Body Mass Index (BMI) and Age on Pregnancy Outcomes at a Tertiary Care Hospital. J Bahria Uni Med Dental Coll. 2023;13(4):271-5 DOI: https://doi.org/10.51985/JBUMDC2023195

INTRODUCTION:

Obesity has become a global phenomenon nowadays and is considered the most common metabolic disorder. Its prevalence has affected the women of reproductive age too.[1] The risks of pregnancy complications such as hypertension, gestational diabetes mellitus, pre-eclampsia, preterm deliveries and birth of growth restricted babies are higher for obese and overweight mothers.[2]

According to the study of Martin et al., pregnancy complications had a statistically direct relationship with overweight, obesity and excessive maternal weight gain during pregnancy which significantly contribute to increased incidence of caesarean section.[3] Women with BMI in the normal range that is (20-24.9kg/m^2) are less likely to have issues conceiving a baby with low risk of miscarriage and stillbirth than those with BMI greater than 25kg/m^2. According to Vince et al., the pregnancy complications associated with obesity and excessive gestational weight gain also include labour complications besides those that are threatening to the lives of mothers and babies.[4]

Zongjiang et al., found out the estimated proportions of unfavourable pregnancy outcomes which were associated with obesity and gestational weight gain. The proportion of GDM was 29.3%, pre-eclampsia was 36.2%, caesarean delivery was 15.5%, 21.6% was longer antenatal stay in hospital with 6.5% of NICU admission, the proportion of births large for gestational age was 25.2% and extreme

Shazia Iffet *(Corresponding Author)*
Assistant Professor, Department of Gyane & Obs
Armed Forces Post Graduate Medical Institute, Rawalpindi
Email: shaziaiffet@gmail.com

Ayesha Arif
Professor, Department of Gyane & Obs
PNS SHIFA Karachi
Email: drayeshaarif2013@yahoo.com

Sadaf Moin
Assistant Professor, Department of Gyane & Obs
Armed Forces Post Graduate Medical Institute, Rawalpindi
Email: sadmoin1992@gmail.com

Aisha Raja
Associate Professor, Department of Gyane & Obs
Karachi Institute of Medical Sciences, Karachi
Email: dr.ayisharaja@gmail.com

Sadia Arif
Associate Professor, Department of Gyane & Obs
PNS SHIFA Karachi
Email: drsadiaarif@hotmail.com

Nadia Arif
Assistant Professor, Department of Gyane & Obs
Armed Forces Post Graduate Medical Institute, Rawalpindi
Email: gyne_drnadia@yahoo.com

Received: 07-05-2023
Accepted: 12-09-2023

preterm births was 16.3%.[5]

Xiu et al. compared the pregnancy outcomes in females with normal pre-pregnancy weights to women with higher BMI and inferred that overweight females before pregnancy had higher risk of preterm birth and that obese women had the greatest risk of extremely preterm births. However, the maternal age and gestational weight gain had low impact on preterm births as the estimators were robust in that case.[6] The effects of age on pregnancy outcomes remain controversial due to several issues such as the effects of maternal weight intervening with the effects of older age. The study done by Malgorzata et al., showed the pregnancy outcomes depending on maternal age substantiating that females related to younger and older age groups had higher adjusted odd ratios of pre-eclampsia, intra uterine growth restriction and preterm births.[7-9] Considering the aforementioned outcomes this study was aimed to assess the effects of maternal BMI and age on pregnancy outcomes in our setup.

METHODOLOGY:

This retrospective cohort study consisted of 500 postnatal women and was carried out over a period of six months from 1st August 2022 to 31st January 2023, at a tertiary care hospital, CMH Abbottabad. According to a WHO calculator with 95% confidence interval, 5% margin of error and a population proportion of 50% a sample size estimated must be greater than or equal to 385 to sufficiently represent unknown population.[8,9] The selection of patients for the data was done through a simple random sampling technique who were booked at first trimester in OPD and were followed up for antenatal care and delivered at CMH Abbottabad. The inclusion criteria composed of the ages of patients that ranged from 19 to 42 years. All primigravida and multigravida were included. The BMI and ages of patients were calculated and recorded at the time of booking visit. The variables also consisted of gestational age, induction (if they were induced or not), spontaneous (if there was a spontaneous onset of labor) and mode of delivery. Exclusion criteria consisted of patients with comorbidities, for example, diabetes mellitus, hypertension and renal parenchymal diseases. Patients aged =42 years or =18 years. It also excludes morbidly obese patients, women with previous 2 scars and with uterine and foetal congenital abnormalities.

The total number of patients with normal BMI were 140 (28%), overweight patients were 310(62%) and obese were 50(10%). Gestational age, induction and spontaneity of labour and mode of delivery were analysed in relation to BMI and age of patients. It was done to assess the importance of maternal weight and age in delivering a baby with less complications during pregnancy and post pregnancy outcomes.

The study was conducted with consent from the patients using consent forms and with permission from the Ethical Institutional Review Board of Combined Military Hospital Abbottabad vide letter no (ERB no CMH Atd-ETH-82-Gyane-23).

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 26. The variables in study consisted of maternal age, BMI, gestational age, induction, spontaneous and mode of delivery. The maternal age was categorized into 3 groups that is =20 years, 21-35 years and 36-42 years. The BMI was classified into 3 categories normal, overweight and obese. They were assigned '1', '2' and '3' labels respectively. The gestational age =37 weeks was categorized as pre-term while greater than 37 weeks was classified as term. The variable induction was assigned a label 'yes' if the patient was induced and 'no' if she was not. The variable spontaneous was also given label 'yes' if the labor was spontaneous and 'no' if it was not. The mode of delivery was categorized into 3 groups that is, instrumental delivery (Ins-D), spontaneous vaginal delivery (SVD) and lower segment caesarean section (LSCS). The chi-sq test was applied to see if there was any effect of maternal BMI and age on the pregnancy outcomes at 5% level of significance.

RESULTS:

During the study 500 patients were assessed since their first trimester throughout the pregnancy till delivery. The age of patients ranged from 19 years to 42 years. The mean age was 32± 11.5 years. The mean BMI was 28.8±8. The total number of patients with normal BMI were 140(28%), the overweight patients were 310(62%) and patients with obesity were 50(10%). Results showed that 129(92.1%) of the females with normal BMI went through spontaneous vaginal delivery whereas this percentage was much lower in overweight and obese patients that is 100(32.3%) and 1(2%) respectively. On the other hand, the number of deliveries through LSCS was much higher in obese patients as compared to normal weight patients. It was 46(92%) in obese and 1(0.7%) in normal patients. Gestational age was divided into two categories. The one with gestational age =37 weeks was called a term birth whereas the one less than or equal to 37 weeks was called preterm births. The preterm births were higher in obese patients that is 8(16%) as compared to normal patients 0(0%). 49 out of 50 patients with obesity required induction and only 1 patient had spontaneous onset of labor. From the results it was evident that BMI had significant relationship with mode of delivery, gestational age, induced or spontaneous labor.

Figure1: Delivery at term according to BMI

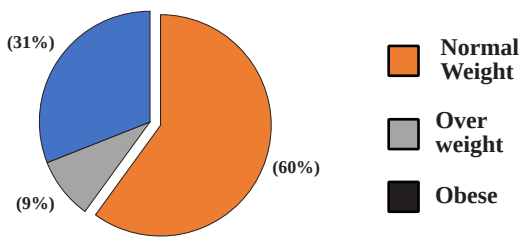


Table 1

Variables	Body Mass Index (BMI)		
	Normal (n=140)	Overweight (n=310)	Obese (n=50)
Mode of Delivery, n(%)			
Ins-D	10 (7.1%)	7 (2.3%)	3 (6.0%)
SVD	129 (92.1%)	100 (32.3%)	1 (2.0%)
LSCS	1 (0.7%)	203 (65.5%)	46 (92.0%)
Gestational Age, n(%)			
Term	140 (100%)	273 (88.1%)	42 (84.0%)
Pre-term	0 (0.0%)	37 (11.9%)	8 (16.0%)
Induction, n(%)			
Yes	35 (25%)	191 (61.6%)	49 (98%)
No	105(75%)	119 (38.4%)	1 (2.0%)
Spontaneous, n(%)			
Yes	105 (75%)	119 (38.4%)	1 (2.0%)
No	35 (25%)	191 (61.6%)	49 (98%)

P-value = 0.000

Figure 2: Mode of Delivery

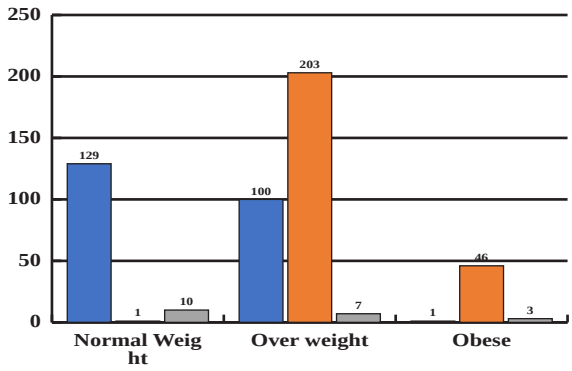


Table 2

Variables	Age Groups		
	=20 years (n=80)	21-35 years (n=275)	36-42 years (n=145)
Mode of Delivery, n(%)			
Ins-D	1 (1.3%)	15 (5.5%)	4 (2.8%)
SVD	14 (17.5%)	160 (58.2%)	56 (38.6%)
LSCS	65 (81.3%)	100 (36.4%)	85 (58.6%)
Gestational Age, n(%)			
Term	76 (95%)	256(93.1%)	123(84.8%)
Pre-term	4 (5%)	19 (6.9%)	22 (15.2%)
Induction, n(%)			
Yes	56 (70%)	127 (46.2%)	92 (63.4%)
No	24 (30%)	148 (53.8%)	53 (36.6%)
Spontaneous, n(%)			
Yes	24 (30%)	148 (53.8%)	53 (36.6%)
No	56 (70%)	127 (46.2%)	92 (63.4%)

P-value = 0.000

The total number of patients in =20 years were 80(16%), in 21-35 years were 275(55%) and in 36-42 years were 145(29%). Most of the patients in younger age group and older age groups went through LSCS. They were 65(81.3%) in =20 years group and 85(58.6%) in 36-42 years group. Whereas they are 100(34.6%) in 21-35 years group. The percentage of preterm births increased in older age group that is 8(16%). Induction required in younger patients were 56(70%) whereas the 24(30%) had spontaneous labor. In older patients 92(63.4%) requires induction where as 53(36.6%) had spontaneous labor. In 21-35 years the incidence of preterm births was 6.9%. In our study induction rate was 46.2% and rate of spontaneous labour was 53.8% where as the required rate of induction world wide should be 20%. The results of chi-sq test is shown in table 1 and table 2. As the p value is less than 0.05 there is a significant relationship between maternal [BMI, age] and pregnancy outcomes [mode of delivery, gestational age, induction and spontaneous].

DISCUSSION:

The implications of obesity associated to pregnancy are often unnoticed and ignored due to the absence of specific evidence based treatment options.[10] It is also ascertained that the management of higher BMI does not require short term initiatives rather a long term sustainable approaches that begin before pregnancy and continue through postpartum period.[11] Furthermore, the timely management is essential to overcome adverse outcomes during pregnancy. Meng et al., showed obesity as one of the prime reasons for emergency CS.[12] In our study the percentage of LSCS in obese patients was higher as compared to females with normal BMI. In normal BMI patients it was 1(0.7%) whereas 46(92%) of the obese patients delivered babies through LSCS. In overweight females it was 203(65.5%). It is evident that maternal BMI does have impact on the mode of delivery because the risk of LSCS increase with increase in BMI.

Buyun et al., explored the effects of maternal BMI on neonatal outcomes and concluded that overweight and obese mothers are at higher risk of giving birth to large for gestational age (LGA) and pre-term babies.[13] In our study the incidence of pre-term births was greater in obese patients. It was 8(16%) as compared to overweight patients 37(11.9%).

Rizwana et al., suggested the induction of labour as a preventive measure for late term stillbirths and caesarean births in obese women with pre-existing complications and comorbidities.[14] However in 20% of the cases induction is not successful in terms of vaginal births and this number increases for some groups such as those with obesity.[15] In our research it is clearly shown that overweight and obese patients had higher rate of induction whereas 75% of the patients with normal BMI had spontaneous onset of labour. Jenny et al., added that the obese patients had lower chance of reaching active stage of labour than leaner patients if they

did not have vaginal delivery previously. However, if they had vaginal delivery then their BMI didn't influence uterine activity. Additionally the risk of caesarean section was lower.[16]

Kumar et al., assessed the relationship between mode of delivery and maternal age and concluded that age effects the mode of delivery because older women tend to have comorbidities which often end up in LSCS.[17] However, some of the studies showed that the incidence of LSCS was more in teenage mothers that is 30% as compared to adult mothers which was 15% (18). This was confirmed by our study too. The number of LSCS was 65(81.3%) in age groups =20 years and in age group 36-42 years it was 85(58.6%) as compared to the group 21-35 years which was 100(36.4%). The incidence of preterm births was higher in older patients as compared to young patients. Alexander put forth the preterm birth as one of the many adverse pregnancy outcomes which are associated with females of advanced maternal age (19). In our study it was found out that 22(15.2%) of the women in advanced age group had preterm births. The rate of induction in the younger age group and older age group was higher as compared to spontaneous onset of labour. Joao et al., showed that in the advanced age group it is higher in order to prevent perinatal deaths which often occur at term in older women (20). In the younger females the successful induction is more prevalent than older women.

CONCLUSION:

There was sufficient evidence that females with higher pre-pregnancy BMI as well as inappropriate weight gain during pregnancy had elevated risks of complications for mother and baby. Therefore, there is a need to increase awareness about the negative effects of inappropriate weight gain in pregnant females and improve management techniques for reproductive age group to avoid adverse outcomes.

Authors Contribution:
Shazia Uffer: Data entry, data analysis
Ayesha Arif: Data collection
Sadaf Moin: Literature search
Aisha Raja: Data analysis
Sadia Arif: Data collection
Nadia Arif: Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data

REFERENCES:

1. Gulam Muhammed Al Kibria, Krystal Swasey, Md Zabir Hasan, Atia Sharmeen, Brendan Day. Prevalence and factors associated with underweight, overweight and obesity among women of reproductive age in India. Glob Health Res Policy. 2019;1(4). https://doi.org/10.1186/s41256-019-0117-z
2. Imran Kutch, iPeriasamy Chellammal, Arthanari Akila. Maternal Obesity and Pregnancy Outcome: in Perspective of New Asian Indian Guidelines. J Obstet Gynecol India. 2020;(70):138–44. https://doi.org/10.1007/s13224-019-01318
3. Hayley Martin, Kelly Thevenet-Morrison, Ann Dozier. Maternal pre-pregnancy body mass index, gestational weight gain and breastfeeding outcomes: a cross-sectional analysis. BMC Pregnancy Childbirth. 2020;1(20):471. https://doi.org/10.1186/s12884-020-03156-8
4. Susana Santos, Ellis Voerman, Pilar Amiano, Henrique Barros, Lawrence J. Beilin. Impact of maternal body mass index and gestational weight gain on pregnancy complications: An individual participant data meta-analysis of European, North American and Australian cohorts. BJOG Int J Obstet Gynaecol. 2019;8(126). https://doi.org/10.1111/1471-0528.15661
5. Zongjian Yang, Hai Phung, Louise Freebairn, Rosalind Sexton, Alexandra Raulli. Contribution of maternal overweight and obesity to the occurrence of adverse pregnancy outcomes. Aust N Z J Obstet Gynaecol. 2018;1(59). https://doi.org/10.1111/ajo.12866
6. Xiu Juan Su, Shi Jia Huang, Xiang Li, Qiao Ling Du. Prepregnancy Overweight and Obesity Are Associated with an Increased Risk of Preterm Birth in Chinese Women. Obes Facts. 2020;2(13):1–8. https://doi.org/10.1159%2F000506688
7. Ma³gorzata Lewandowska, Stefan Sajdak, Barbara Wiêckowska, Nevena Manevska, Jan Lubinski. The Influence of Maternal BMI on Adverse Pregnancy Outcomes in Older Women. Nutrients. 2020;9(12). https://doi.org/10.3390/nu12092838
8. Saccone G, et al.Int J Gyanecol Obstet.2022.PIMD:35044694 Free PMC article. Review.
9. Farhad Islami, Farin Kamangar. Sample Size Calculation for Epidemiologic Studies: Principles and Methods. Arch Iran Med. 2013;5(16):295–300.
10. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Obesity in Pregnancy: ACOG Practice Bulletin, Number 230. Obstet Gynecol. 2021;6(137):e128–44.
11. Fionnuala M. McAuliffe, Sarah Louise Killeen, Chandni Maria Jacob, Mark A. Hanson, Eran Hadar, H. David McIntyre, Anil Kapur, Anne B. Kihara, Ronald C. Ma, Hema Divakar, Moshe Hod. Management of prepregnancy, pregnancy, and postpartum obesity from the FIGO Pregnancy and Non-Communicable Diseases Committee: A FIGO (International Federation of Gynecology and Obstetrics) guideline. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2020;1(S1):16–36. https://doi.org/10.1002/ijgo.13334
12. Meng LiChun, Yi ZhangChao, Yan Yue. Effects of pre-pregnancy BMI and gestational weight gain on adverse pregnancy outcomes and complications of GDM. J Obstet Gynaecol. 2022;4(42):1–6. https://doi.org/10. 1080/ 01443615 .2021.1945009
13. Buyun Liu, Guifeng Xu, Yangbo Sun, Yang Du, Rui Gao. Association between maternal pre-pregnancy obesity and preterm birth according to maternal age and race or ethnicity: a population-based study. Lancet Diabetes Endocrinol. 2019;9(7). https://doi.org/10.1016/s2213-8587(19)30193-7
14. Rizwana Ashraf, Cynthia Maxwell, Rohan D'Souza. Induction of labour in pregnant individuals with obesity. Bailliegrave Re Best Pract Res Clin Obstet Gynaecol. 2022;79:70–80. https://doi.org/10.1016/j.bpobgyn.2021.12.004
15. U Dammer, Roswitha Bogner, Christel Weiss, F Faschingbauer, Jutta Pretscher. Influence of body mass index on induction of labor: A historical cohort study: Influence of BMI on labor induction. J Obstet Gynaecol Res. 2018 Jan;Pt 2(44). https://doi.org/10.1111/jog.13561

16. Jenny Bjorklund, Eva Wiberg-Itzel, Tove Wallstrom. Is there an increased risk of cesarean section in obese women after induction of labor? A retrospective cohort study. PLoS ONE. 2022;2(17). https://doi.org/10.1371%2Fjournal.pone.0263685

17. SunilKumar Juneja, Pooja Tandon, Gagandeep Kaur. To Evaluate the Effect of Increasing Maternal Age on Maternal and Neonatal Outcomes in Pregnancies at Advanced Maternal Age. Int J Appl Basic Med Res. 2022;4(12):239. https://doi.org/10.4103/ijabmr.ijabmr_193_22

18. Sandeep Dhore, Aparna Wahane, Pratiksha Gaikwad, Rutuja Sawalsurkar, Harshal Shankar Warke. A Study of Teenage Pregnancy Its Risk Factors And Complications At The Tertiary Care Center. Int J Sci Res. 2023;12(2). https://www.doi.org/10.36106/ijsr/6009647

19. Alexander M. Saucedo, Alison G. Cahill. Evidence-Based Approaches to Labor Induction. Obstet Gynecol Surv. 2023 ;3(78):171–83. https://doi.org/10.1097/ogx.0000000000001110

20. Maria João Fonseca, Fernanda Santos, Vera Afreixo, Isabel Santos Silva, Maria do Céu Almeida. Does induction of labor at term increase the risk of cesarean section in advanced maternal age? A Systematic Review and Meta-Analysis. Eur J Obstet Gynecol Reprod Biol. 2020;4(253). https://doi.org/10.1016 /j.ejogrb.2020.08.022

Original Article **Open Access**

Frequency of H-Pylori Infection in Immune Thrombocytopenic Purpura

Aqsa Javed Butt, Uzma Zaidi, Muhammad Shujat Ali, Rabeea Munawar Ali, Sidra Zafar, Tahir Shamsi

ABSTRACT

Objective: To determine the frequency of Helicobacter pylori infection in patients with Immune Thrombocytopenia (ITP) and the impact of eradication therapy on platelet counts.

Study design & Setting: It was a cross-sectional study conducted at National institute of blood disease and bone marrow transplant (NIBD) hospital, Karachi, Pakistan from January 2021 to September 2022.

Methodology: Adults between 18 to 70 years of either gender with thrombocytopenia (platelet count less than $100x10^9$/L) with or without bleeding manifestation from last six months were recruited. The immunoassay was used for stool sample to detect *H. pylori* antigen, eradication therapy was administered and platelet counts were evaluated at 3rd and 6th month of treatment.

Results: Of 120 patients with ITP, the mean age was 36.67±15.32 years, and 76.7% were female. 35.83% had H. pylori positive. The eradication treatment on platelet counts was statistically significant (p=0.001). Median platelet counts at baseline, 3 months and 6 months were 43.50(23.00- 77.00), 136.50 (57.00- 237.00), and 192.00 (130.50-275.50) patients respectively. Platelet counts were statistically different between baseline with three and six months (p=0.007 and p=0.001, respectively).

Conclusion: People with ITP frequently have H. pylori infections, and eradication treatment could contribute to the increase in platelet count.

Keywords: Bacteria, Eradication, *H. pylori*, ITP, Platelet count

How to cite this Article:

Butt AJ, Zaidi U, Ali MS, Ali RM, Zafar S, Shamsi T. Frequency of H-Pylori Infection in Immune Thrombocytopenic Purpura. J Bahria Uni Med Dental Coll. 2023;13(4):276-80 DOI: https://doi.org/10.51985 /JBUMDC2023206

Aqsa Javed Butt *(Corresponding Author)*
Resident, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: aqsa_butt21@yahoo.com

Uzma Zaidi
Consultant, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: uzaidi26@gmail.com

Muhammad Shujat Ali
Resident, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: Shujaatali1991@gmail.com

Rabeea Munawar Ali
Resident, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: rabeea_ali@hotmail.com

Sidra Zafar
Clinical Research Associate, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: sidrazfr@gmail.com

Tahir Shamsi
HOD Clinical Hematologist, Department of Clinical Hematology
National Institute Of Blood Disease and Bone Marrow Transplant
Email: t.shamsi.62@gmail.com

Received: 30-05-2023
Accepted: 12-09-2023

INTRODUCTION:

Immune thrombocytopenia (ITP), is characterised by isolated thrombocytopenia (platelet count $<100 \times 10^9$/L) without a known cause.[1] IgG autoantibodies that target structural platelet membrane glycoproteins IIb–IIIa are thought to be the cause of ITP.[2]This makes platelets vulnerable to being phagocytized by Kupffer cells in the liver and splenic macrophages.These autoantibodies are present in 40-60% of affected individuals.Other mechanism like impaired production of a stimulant of platelet production called thrombomodulin and triggers like exposure to viruses and pregnancy are also likely causes of ITP[2].Usuallly in ITP studies, H-pylori antigen, Hepatitis C, a peripheral blood smear and HIV testing are essential investigations.[2] The timing and persistence of symptoms are used to further divide primary ITP into three stages i.e. newly diagnosed ITP (with less than 3 months of duration), Chronic ITP is the continuation of ITP beyond the initial diagnosis of 3 to 12 months, whereas persistent ITP is the referring to low platelet count for more than 3-12 months.[3]

A gram-negative bacterium called Helicobacter pylori (H. pylori) was initially discovered by Warren et al. in 1984.[4] It occurs in the human stomach. Most of the individuals remain asymptomatic for a long time. As a result, long term

colonization will lead to damage of gastric mucosa causing peptic ulcers, chronic gastritis, atrophic gastritis gastric malignancies like mucosa-associated lymphoid tissue lymphoma, gastric cancer.[5] Although the pathogenesis of H. pylori-associated ITP is still uncertain, several studies have suggested that H. pylori virulence factor, cytotoxin-associated gene A (CagA), stimulates the development of anti-CagA antibodies (Abs) that cross-react with platelet surface antigens (Ags), resulting in thrombocytopeni.[3,7] Its prevalence is highest in African countries (79%), Caribbean and Latin America (63%), and Asia (55%).[6] Pakistan has the greatest frequency of H. pylori among South Asian countries, followed by Nepal (70%) and India (64%), respectively.[6] Food and hygiene, age, socio-economic status, ethnicity, number of siblings, household crowding, sanitary facilities, infection status of family members, and migration from high prevalence regions are known risk factors of H pylori.[7,8]

Many research studies have revealed significant correlation between H pylori and extra-digestive diseases like iron deficiency anemia, vitamin B12 deficiency, and ITP.[4,5,8,9] Autoantibodies against platelets cause the acquired bleeding illness known as ITP, which impact all ages.[10,11] It may be a primary or secondary disease brought on by neoplasms, autoimmune disorders, viral or bacterial infections, or both.[10,11]

Literature found that individuals with ITP had higher proportion of H. Pylori.[4,5,11] Additionally, it has been seen that H. pylori significantly impact the pathophysiology due to the complete or partial recovery of thrombocytopenia following H. pylori eradication.[4,5,11] So, one of the treatments for ITP is the eradication of H. pylori infection.[4,11]

The purpose of the current study was to ascertain how frequently H. pylori is present in patients with immune thrombocytopenic (ITP) who report to a tertiary care hospital in Karachi, Pakistan, as well as the impact of eradication therapy on platelet count. The results of this study would enable the development of guidelines for the identification and eradication of H. pylori in ITP patients.

METHODOLOGY:

This was a cross-sectional study carried out at the department of Haematology NIBD, Karachi, Pakistan from January 2021 to September 2022. Sample size of 115-120 patients with ITP was estimated using Open epi sample size calculator, by taking prevalence of H pylori as 40.9%, bond on error as 9% and 95% confidence level. The study comprised patients with a platelet count<$100x10^9$/L who had thrombocytopenia with or without bleeding and were between the ages of 18 and 70. The research excluded patients having a history of malignancy, disseminated intravascular coagulation, bone marrow failure, hypersplenism, or who were receiving drug therapy that was known to cause thrombocytopenia. The approach of non-probability consecutive sampling was used.

The NIBD ethical review committee approved this study (NIBD/IRB-254/26-2021). A written informed consent was taken from all the eligible participants. On a pre-made proforma, information on patient's age, gender, diseases, and comorbid conditions including diabetes and hypertension were collected. On a stool sample, the immunoassay technique was used, and the H. pylori antigen was detected. For haematological assessment (haemoglobin, TLC, and platelet counts), blood was drawn from the patients in EDTA tube, and the CBC was done. In H. pylori positive cases, eradication therapy was given (Cap Omeprazole 20mg twice daily, Tablet Clarithromycin 500mg twice daily and Tab Amoxil 1gm twice daily for 14 days) and platelet counts were evaluated at 3rd and 6th month of treatment.

Statistical analysis was carried out using SPSS version 23. Mean and SD/Median and IQR were reported for numeric variables like age, Hb, TLC and platelet counts. For categorical characteristics including gender, illness type, comorbid, and H. pylori, frequency and percentage were provided. H. pylori were stratified with age, gender, disease nature, comorbids, Hb, TLC and platelet counts. Post-stratification Chi-square test, Independent t-test or Mann-Whitney U test/ were applied. Effect of eradication therapy was assessed by comparing platelet counts at baseline, three months and six months using Friedman test and post hoc pair-wise comparison was done. Level of significance for this study was set at 5%.

RESULTS:

Baseline characteristics of ITP patients are displayed in table 1. Of 120 patients, 76.7% were females, with mean age as 36.67±15.32 years. At baseline, the mean hemoglobin was 12.09±2.22, median TLC was 8.81 and median platelet was 40x 10^9. Most frequent comorbid was hypertension.

Insignificant statistical difference was found with a p-value higher than 0.05 when comparing the ITP patients with and without H. pylori in terms of age, gender, comorbid, or hematological parameters (Table 2).

Out of 120 patients, 35.83% (43/120) tested positive for H. pylori while 64.17% (77/120) were negative for H. pylori. The significant effect of eradication therapy of H. pylori positive cases (p=0.001) had been observed on platelet counts. In H pylori positive cases, median platelet counts at baseline, 3 months and 6 months were 43.50 (23.00-77.00), 136.50 (57.00-237.00), and 192.00 (130.50-275.50), respectively. There was a statistically significant difference observed in platelet counts at baseline versus 3 months (p=0.007) and baseline versus 6 months (p=0.001). However, the difference was insignificant when platelet counts at 3 months versus 6 months (p=0.055) were compared. In H pylori negative cases, median platelet counts at baseline, 3 months and 6 months were 36.0 (18.0-60.0), 94.0 (36.5-221.5), and 83.0 (33.0-197.0), respectively. Statistically significant difference was observed in platelet counts at

baseline versus 3 months (p=0.026). However, there was insignificant difference observed in platelet counts at baseline versus 6 months (p=0.068) and at 3 months versus 6 months (p=0.999).

Table 1: Descriptive analysis of enrolled ITP patients (n=120)

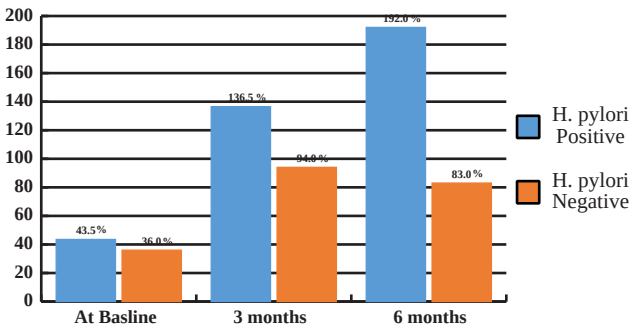
Variables	
Age (years)	36.67±15.32
Hemoglobin at baseline (g/dL)	12.09±2.22
TLC at baseline (x10^9/L)	8.81 (6.66-11.73)
Platelet at baseline (x10^9/L)	40 (17.5-75)
Gender	
Female	92 (76.7)
Male	28 (23.3)
Hypertension	
Yes	23 (19.2)
No	97 (80.8)
Diabetes	
Yes	20 (16.7)
No	100 (83.3)

Data showed in the form of Mean±SD or Median (IQR) or n (%)

Table 2: Comparison of baseline characteristics between H. pylori positive and negative in ITP (n=120)

	H. pylori		**p-value**
	Positive	**Negative**	
Age (years)	36.51±16.06	36.75±15	0.934
Hb g/dl at baseline	11.77±2.11	12.26±2.26	0.259
TLC x10^9/l at baseline	9.30 (7.74-12.12)	8.65 (6.40-11.62)	0.336
PLT x10^9/l at baseline	43.50(23.00-77.00	36.0(18.0-60.0)	
Gender			
Male	13 (46.4)	15 (53.6)	0.182
Female	30 (32.6)	62 (67.4)	
Hypertension			
Yes	8 (34.8)	15 (65.2)	0.907
No	35 (36.1)	62 (63.9)	
Diabetes mellitus			
Yes	6 (30)	14 (70)	0.551
No	37 (37)	63 (63)	

Figure 1: Comparison of platelet counts at baseline, 3 months and 6 months in patients with and without H. pylori



DISCUSSION:

Since many years, H Pylori has been considered as the one of the reason of peptic ulcers, mucosa-related lymphoma, gastritis and gastric cancer.[14,16-17] Recent research has revealed a link between h-pylori and autoimmune conditions such ITP[14,16-17]. According to studies, H pylori is a frequent cause of ITP and that treatment for the infection typically results in a rise in platelet count in most cases.[11-14,18]

The frequency of H. pylori among cases of ITP varied greatly between different countries. It is reported as 73% in Japan, 51% in Italy, 54.3% in Korea, 22% in Malaysia and in Northern America.[5,11,12,14-15] Twenty-seven studies from across the world were merged and analysed, and the results showed that 1144 out of 1740 individuals with ITP had H. pylori infection, or 65.7% of the total.[14] In addition, Ando et al. discovered that 83% of patients with ITP had a higher proportion of H pylori infection.[19] In our study, we found 42.3% of the ITP patients had H pylori.[15] Kakar et al. discovered that the proportion of H pylori was 40.5% in cases of ITP in a comparable Pakistani investigation. While in another Pakistani study by Shaikh et al. its prevalence is 63.3% in ITP.[14] The frequent occurrence of H. pylori infection in underdeveloped countries can be due to socio-economic background and living conditions of the patients.

Several studies have found insignificant relationship with demographic and clinical factors in patients with ITP.[20] In our study, we also found no significant association of age, gender, haematological parameters, duration of disease and comorbid with H. pylori infection in patients with ITP. We found the frequency of H. pylori was high in females as compared to males, which may be due to high prevalence of ITP in females. Furthermore, average age of H. pylori positive and negative cases was similar. Similar results have been presented for Pakistani Population in the study by Kakar et. i.e. there was no difference in H. pylori frequency with respect to gender and age. Whereas, some international studies showed that the mean age of H. pylori patients having ITP was greater than uninfected patients.[19-21]

In the study by Gasbarrini et al. found that platelet counts remained unchanged in three H. pylori patients who were not treated for eradication, whereas, in eight H. pylori patients, platelet counts increased post ITP treatment.[22] In another nation-wide study conducted in Japan including 207 patients with H. pylori infection showed that 63% of the patients achieved some platelet recovery and in this group 23% of the patients achieved complete remission after 1 year of eradication therapy.[21] In our study, we found that median platelet count was low in patients without infection as compared to patients with infection. We also found significant effect of eradication therapy on platelet counts

in H. pylori patients with ITP after 3 months. Similarly, Kakar et al. also stated that mean platelet count was high in infected patients as compared to uninfected patients.[15] In a recent research by Sheema et al., positive H pylori patients had slightly lower platelet counts than controls.[23] Gan CC et al. found that patients with H. pylori had higher platelet counts than baseline controls in the Malaysian population[24]. Although Hwang JJ et al. noted a statistically negligible difference in platelet count between patients with ITP who had H. pylori positivity and those who did not prior to eradication treatment.[25]

There are few limitations of current study. This is a cross-sectional study, in which we are unable to assess the cause effect relation between H pylori and ITP. We were unable to identify the consequence of haematological parameters, socio-demographic factors, and comorbid on *H. pylori* due to small size. In future, long-term studies should be conducted as well as effect of eradication therapy and bacterial strains should be explored.

CONCLUSION:

People with ITP frequently have H. pylori infections, and eradication treatment has a considerable impact on platelet count in ITP patients. Therefore, in patients with ITP at diagnosis, screening for H. pylori infection and attempt to eradicate the bacteria in positive cases appears to be a good approach.

Authors Contribution:
Aqsa Javed Butt: reviewed all the cases for inclusion, data collection, statistical analysis, drafted this article
Uzma Zaidi: conceptualized and supervised the study, reviewed all the cases for inclusion, critically reviewed the manuscript
Muhammad Shujat Ali: Data Collection
Rabeea Munawar Ali: Data Collection
Sidra Zafar: Data Collection
Tahir Shamsi: Conceptualized and supervised that study.

REFERENCES:

1. McCRAE KE. Immune thrombocytopenia: no longer 'idiopathic'. Cleveland Clinic journal of medicine. 2011 Jun;78(6):358. doi: 10.3949/ccjm.78gr.10005
2. Zainal A, Salama A, Alweis R. Immune thrombocytopenic purpura. Journal of community hospital internal medicine perspectives. 2019 ;9(1):59-61. doi.org/10.1080/ 20009666. 2019.1565884
3. Justiz Vaillant AA, Gupta N. ITP-Immune Thrombocytopenic Purpura.[Updated 2022 Jul 8]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022.
4. Barbosa AM, Ribeiro RA, Silva CÍ, Cruz FW, Azevedo OG, Pitombeira MH, Braga LL. Platelet count response to Helicobacter pylori eradication for idiopathic thrombocytopenic purpura in northeastern Brazil. Hematology, Transfusion and Cell Therapy. 2018;40:12-7. https://doi.org/10.1016/ j.bjhh. 2017.09.005
5. Ikuse T, Toda M, Kashiwagi K, Maruyama K, Nagata M, Tokushima K, Ito N, Tokita K, Kyodo R, Hosoi K, Jimbo K. Efficacy of Helicobacter pylori eradication therapy on platelet recovery in pediatric immune thrombocytopenic purpura-Case series and a systematic review. Microorganisms. 2020;8(10):1457. doi.org/10.3390/microorganisms8101457
6. Hooi JK, Lai WY, Ng WK, Suen MM, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VW, Wu JC, Chan FK. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):420-9. https://doi.org/10.1053/ j.gastro.2017.04.022
7. Khoder G, Muhammad JS, Mahmoud I, Soliman SS, Burucoa C. Prevalence of Helicobacter pylori and its associated factors among healthy asymptomatic residents in the United Arab Emirates. Pathogens. 2019;8(2):44. https://doi.org/10.3390/ pathogens8020044
8. Venneman K, Huybrechts I, Gunter MJ, Vandendaele L, Herrero R, Van Herck K. The epidemiology of Helicobacter pylori infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: A systematic review. Helicobacter. 2018;23(3):e12483. https://doi.org/10.1111/hel.12483
9. Muhammad JS, Zaidi SF, Saeed SA, Ishaq M. Current status of Helicobacter pylori association with haematological and cardiovascular diseases: A mini review. Journal of Pakistan Medical Association. 2017;67(6):907.
10. TAN HJ, GOH KL. Extragastrointestinal manifestations of Helicobacter pylori infection: facts or myth? A critical review. Journal of Digestive Diseases. 2012;13(7):342-9. https://doi.org/10.1111/j.1751-2980.2012.00599.x
11. Kim BJ, Kim HS, Jang HJ, Kim JH. Helicobacter pylori eradication in idiopathic thrombocytopenic purpura: a meta-analysis of randomized trials. Gastroenterology research and practice. 2018;2018. https://doi.org/10.1155/2018/6090878
12. Antony A, Karthick R, Ali M, Chenthil K. Prevalence of H. pylori in Immune Thrombocytopenic Purpura (ITP) in a tertiary care center, South India.
13. Ihtesham A, Maqbool S, Nadeem M, Janjua MB, Sundus O, Naqqash AB, Mohamed WI, Haider ST, Ahmad M, Mustafa MA, Mehboob HO. Helicobacter pylori induced Immune Thrombocytopenic Purpura and perspective role of Helicobacter pylori eradication therapy for treating Immune Thrombocytopenic Purpura. AIMS microbiology. 2021;7(3):284. doi: 10.3934/microbiol.2021018
14. Shaikh KH, Ahmed S, Ayyub M, Anwar J. Association of Helicobacter pylori infection with idiopathic thrombocytopenic purpura. JPMA. The Journal of the Pakistan Medical Association. 2009;59(10):660.
15. Kakar JU, Sultan S, Irfan SM, Zeeshan R, Rabbani U. Frequency of Helicobactor pylori infection among adult patients with chronic immune thrombocytopenia: A Pakistani Perspective. Journal of Applied Hematology. 2014;5(2):54. DOI: 10.4103/1658-5127.137144
16. Keikha M, Sahebkar A, Yamaoka Y, Karbalaei M. Helicobacter pylori cagA status and gastric mucosa-associated lymphoid tissue lymphoma: a systematic review and meta-analysis. Journal of Health, Population and Nutrition. 2022;41(1):1-1.

17. Wroblewski LE, Peek Jr RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clinical microbiology reviews. 2010 Oct;23(4):713-39. DOI: https://doi.org/10.1128/cmr.00011-10

18. Campuzano-Maya G. Proof of an association between Helicobacter pylori and idiopathic thrombocytopenic purpura in Latin America. Helicobacter. 2007 Jun;12(3):265-73. https://doi.org/10.1111/j.1523-5378.2007.00502.x

19. Ando K, Shimamoto T, Tauchi T, Ito Y, Kuriyama Y, Gotoh A, Miyazawa K, Kimura Y, Kawai T, Ohyashikia K. Can eradication therapy for Helicobacter pylori really improve the thrombocytopenia in idiopathic thrombocytopenic purpura? Our experience and a literature review. International journal of hematology. 2003 Apr;77:239-44.

20. Kuwana M. Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. World Journal of Gastroenterology: WJG. 2014 Jan 1;20(3):714. doi: 10.3748/wjg.v20.i3.714

21. Fujimura K, Kuwana M, Kurata Y, Imamura M, Harada H, Sakamaki H, Teramura M, Koda K, Nomura S, Sugihara S, Shimomura T. Is eradication therapy useful as the first line of treatment in Helicobacter pylori-positive idiopathic thrombocytopenic purpura? Analysis of 207 eradicated chronic ITP cases in Japan. International journal of hematology. 2005 Feb;81:162-8.

22. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. The Lancet. 1998 Sep 12;352(9131):878. DOI:https://doi.org/10.1016/S0140-6736(05)60004-9

23. Sheema K, Ikramdin U, Arshi N, Farah N, Imran S. Role of Helicobacter pylori eradication therapy on platelet recovery in chronic immune thrombocytopenic purpura. Gastroenterology Research and Practice. 2017 Jan 17;2017. https://doi.org/10.1155/2017/9529752

24. Gan GG, Norfaizal AL, Bee PC, Chin EF, Habibah AH, Goh KL. Helicobacter pylori infection in chronic immune thrombocytopenic purpura patients in Malaysia. Med J Malaysia. 2013 Jun 1;68(3):231-3.

25. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. The effects of Helicobacter pylori eradication therapy for chronic idiopathic thrombocytopenic purpura. Gut and Liver. 2016 May;10(3):356. doi: 10.5009/gnl14483

Original Article **Open Access**

Preventing NASH with Empagliflozin and Linagliptin: A Diabetic Drug Combination

Asma Abdul Razzak, Pervez Ashraf

ABSTRACT:

Objective: To determine the effect of anti-diabetic drug combination of 25mg empagliflozin and 5mg linagliptin for the prevention of NASH.

Study Design & Setting: Quasi-Experimental Study design, Department of Gastroenterology, Medicare Cardiac and General Hospital Karachi from October 2022 to March 2023.

Methodology: This study was carried out after approval from the ethical board of the hospital. The selection criteria of patients included positive family history of obesity, hyperlipidemia/ hypertriglyceridemia, hypothyroidism, smoking and F3 Fibrosis on transient elastography. The initial screening of clinical history, physical examination, laboratory findings were recorded after taking the written consent from each patient. The baseline findings were recorded and the effect of drugs was examined after follow-up of six months.

Results: The study included 150 patients who received the treatment of empagliflozin and linagliptin. The mean age of these patients was 37±4.9 years. Majority of them were males 76% and 60% were diagnosed type 2 diabetes more than 5 years ago. Hyperglycemia and hypoglycemia were found in 16.7% in patients with headache of 26.7%. The baseline findings were significantly changed with effective and favorable results as p-value<0.001.

Conclusion: The treatment with combine effect of the antidiabetic drugs empagliflozin (25 mg) and linagliptin (5 mg) showed a safety profile of preventing NASH with the fixed dose. It reduced the ALT and AST levels, reduced BMI, triglyceride level, HBA1C and the risk of progression of advance liver disease NASH. After taking antidiabetic drugs, Fibrosis was improved and it showed F1–F2 on transient elastography.

Keywords: Anti-diabetic drugs, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis.

How to cite this Article:
Razzak AA, Ashraf P. Preventing NASH with Empagliflozin and Linagliptin: A Diabetic Drug Combination. J Bahria Uni Med Dental Coll. 2023;13(4):281-5 DOI: https://doi.org/10.51985/JBUMDC2023227

INTRODUCTION:

Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD). Increase of fat in the liver is the root cause of NAFLD and when it damages and inflames the liver, it results in NASH, which can cause liver scarring. The prevalence of NAFLD and NASH is reported in different research with an abundance of diversity.[1] The prevalence of non-alcoholic fatty liver disease (NAFLD), which affects an estimated one-fourth of adults globally, has made it a severe public health issue. According to estimates, 3-5% of the world's population suffers NASH, with the majority experiencing several comorbidities. Clinical outcomes are influenced by progressing fibrosis, 20% of patients will develop cirrhosis and/or HCC, with the latter being the main cause of death in NASH.[2] Up to 30% of NAFLD patients develop non-alcoholic steatohepatitis (NASH), which is characterized by hepatic lipid deposition (steatosis), lobular inflammation, hepatocellular ballooning, and fibrosis. NAFLD and NASH both have a 25.2% and a 1.5–6.45% global prevalence, respectively.[3] The chances of developing NASH rises with age. It is still not entirely identified how gender variations affect the likelihood of developing NASH.[4]

NASH and diabetes mellitus are two distinct yet closely interconnected metabolic disorders that have garnered significant attention due to their escalating global prevalence and their intricate impact on human health. Due to its strong association with diabetes and its potential to elevate the risk of serious complications such as hepatocellular carcinoma (HCC) and cirrhosis, NASH can be referred to as "Diabetic Liver Disease".[5] The changes in glucose and lipid metabolism, insulin resistance (IR), and insulin secretion are the key pathophysiological mechanisms driving the development of NAFLD, which accounts for the strong relationship between NAFLD and Type 2 diabetes.[6] In Japan, type 2 diabetes (T2D) mortality is mostly triggered by liver disorders,

Asma Abdul Razzak *(Corresponding Author)*
Assistant Professor, Department of Gastroenterology
Medicare Cardiac and General Hospital
Email: dr.asmabofficiall@gmail.com

Pervez Ashraf
Consultant, Department of Gastroenterology
Liaquat National Hospital
Email: Pervez_ashraf53@hotmail.com

Received: 31-07-2023
Accepted: 18-09-2023

accounting for 9.3% of all deaths. The strong interconnection between nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D) underscores their status as two of the most prevalent chronic health conditions worldwide. NAFLD, a widely prevalent liver ailment and T2D, a common metabolic disorder, are intricately linked, showcasing a substantial relationship between these two health issues.[7]

The importance of vitamin E as a fundamental therapy option, particularly for people without diabetes, has been shown by extensive research and clinical investigations. With patients who have severe fibrosis, this therapeutic approach has shown tremendous promise in preventing the course of liver disease. The importance of this approach rests in its capacity to stop liver problems from progressing to critical stages that could cause hepatic decompensation or require transplantation.[8] Vitamin E, a fat-soluble antioxidant, plays a vital role in protecting cells from oxidative stress and inflammation. In the context of nonalcoholic fatty liver disease (NAFLD) and its more advanced form, nonalcoholic steatohepatitis (NASH), oxidative stress and inflammation are key contributors to disease progression. Severe fibrosis represents a critical stage in the progression of NAFLD and NASH, often associated with increased risk of liver-related complications. Vitamin E by itself had no discernible effect on the key histology result in T2D patients with NASH. Combination of vitamin E and pioglitazone is more effective than a placebo for enhancing liver histology in NASH patients with diabetes.[9] Metformin remains the recommended first-line treatment for type 2 diabetes, even though its direct impact on NAFLD and NASH might be limited. Its well-established benefits in diabetes management, safety profile and potential ancillary advantages make it a valuable tool in the comprehensive approach to treating individuals with type 2 diabetes.[10-12]

The synergistic approach of combining linagliptin with empagliflozin, complemented by a balanced and nutritious diet, and consistent physical activity, forms a comprehensive strategy to effectively manage elevated blood sugar levels associated with diabetes. Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, aids in maintaining stable blood sugar levels by inhibiting the breakdown of incretin hormones which stimulate insulin release and suppress glucagon secretion. Empagliflozin, on the other hand, is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that promotes the elimination of excess glucose through urine, reducing its reabsorption in the kidneys.

This combination leverages the distinct mechanisms of action of linagliptin and empagliflozin to target multiple aspects of glucose regulation within the body. Additionally, it helps individuals with type 2 diabetes, heart disease, and blood vessel disease reduce their risk of mortality. In the kidneys, empagliflozin helps to stop the absorption of glucose, the blood sugar. By raising the amounts of chemicals in the body that cause the pancreas to produce more insulin, linagliptin aids with blood sugar regulation. When there is excessive sugar in the blood, it also warns the liver to stop generating sugar.[13] By eating a balanced diet and keeping a healthy weight, people may be able to avoid them. Changing your diet and losing weight may be advised by the doctor if someone is suffering from NAFLD. Research on several diseases and conditions is conducted and supported by the National Institutes of Health (NIH), including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[14]

Combination therapy of currently available anti-diabetic medications will probably lead to better effectiveness in the future by addressing a variety of key pathways in the development of NASH. If SGLT2 inhibitors are used as the first-line therapy for NASH/NAFLD, there is a risk that this will worsen the condition since hyperglucagonemia can play significant roles in the etiology of the disease. This experimental study aimed to determine the effect of anti-diabetic drug combination of empagliflozin and linagliptin for the prevention of NASH. This research will explore the indirect prevention of treating chronic liver disease NAFLD and to prevent NASH.

METHODOLOGY:

A quasi-experimental study was systematically undertaken at the Medicare Cardiac and General Hospital located in Karachi. Prior to the initiation of the study, ethical approval was diligently sought and obtained from the relevant ethical review board, ensuring that the research adhered to established ethical standards and guidelines. The data collection period spanned from October 2022 to March 2023, encompassing a duration of six months. During this time, diabetic patients who also presented with liver disease were identified and included as participants in the study. The criteria used for the selection of patients encompassed several key factors. These factors included the presence of F3 Fibrosis as determined through transient elastography, a positive family history of obesity, an elevated Body Mass Index (BMI) exceeding 25, the presence of hyperlipidemia or hypertriglyceridemia, a diagnosis of hypothyroidism, a history of smoking, and a lifestyle characterized by physical inactivity and sedentary habits. The parameters guiding the exclusion of participants were meticulously defined to ensure the integrity of the findings of the study. Pregnant women, due to the unique physiological state of pregnancy, were purposefully omitted from the participant to maintain a focused investigation on the selected variables. Similarly, individuals grappling with malignancy, sepsis, pancreatitis and allergies were excluded from the study. The calculated sample size by using Openepi and keeping 95% confidence interval was 17 from the study . They reported that 1.1% patients will suffer from liver disease by taking the combination of empagliflozin + linagliptin. The sample size will be increased up to 150 to precise the results.

The initial screening of clinical history, physical examination, laboratory findings and HBA1C of more than 9% were recorded after taking the written consent from each patient. The antidiabetic drug used in the study was the combination of empagliflozin and linagliptin. The study medicines were given as per the routine administration policy by the primary author. The baseline findings were recorded and the effect of drugs was examined after follow-up of six months.

IBM SPSS version 21.0 and Microsoft Excel 2013 were employed as the analytical platforms. For continuous variables, such as age, the analysis hinged on utilizing the mean accompanied by its corresponding standard deviation (SD). Numbers with percentages was used for categorical variables such as gender, group etc. The pre/post analysis was undertaken using the paired t-test, a statistical method adept at assessing the significance of differences within paired data points and the significance was determined by the p-value, with a threshold set at less than 0.05.

RESULTS:

The research involved a total of 150 diabetic patients who underwent treatment using both empagliflozin and linagliptin. The average age of these patients was calculated to be 37 years, with a standard deviation of 4.9 years. The age range spanned from 22 to 45 years. A notable predominance of male patients was observed, with 114 individuals (76%), while the remaining 36 patients (24%) were female. The average BMI of patients was 27.5±1.6 with the majority lied between 25 and 30. 60% were diagnosed type 2 diabetes more than 5 years ago.

Within the spectrum of adverse events, the recorded occurrences encompassed instances of both hyperglycemia and hypoglycemia with 25 cases (16.7%). A noteworthy observation emerged, indicating that the predominant adverse reaction among the participants was headache, with a substantial 40 instances (26.7%) reported. Almost half of the patients were not taking concomitant oral anti-diabetic drugs.

Table 1 presents the treatment effects of a combination of anti-diabetic drugs before and after intervention. The baseline findings of all the 150 patients were presented in detail which showed significantly changed with effective and favorable results as p-value<0.05.

The p-values indicated that the observed changes in all these parameters are statistically significant, implying that the intervention had a notable impact on these measures. The table succinctly presents the quantitative changes in these parameters before and after the anti-diabetic drug combination intervention, showcasing the effectiveness of the treatment.

DISCUSSION:

Recent research has revealed a strong, reciprocal link between diabetes and NASH. Despite the complexity of the relationship between these things, a number of fundamental mechanisms have been put forth that include common pathophysiological processes such adipokine dysregulation, oxidative stress, inflammation, and insulin resistance. World Health Organization (WHO) should be evaluated for NASH-fibrosis for the current guidelines[16,17] as it is still unclear. Despite suggesting "consider screening" in cases of high risk patients, such as those with obesity and metabolic syndrome or type 2 diabetes, they oppose systematic screening due to the knowledge gaps regarding the cost-effectiveness of this method. It is understandable that there is a conflicting message regarding screening and intervention because there is insufficient information on how early intervention affects the course of steatohepatitis.[18] There is a critical need for novel insulin sensitizers because the pathophysiology of both T2D and NASH is largely influenced by insulin resistance. Although Peroxisome proliferator-activated receptor (PPAR) agonists, particularly PPARy and pan-PPARs agonists have demonstrated some positive benefits on both NASH and liver fibrosis. The frequent use of these agents should be constrained by their safety profile. The most effective anti-diabetic medications for NASH treatment are incretin-based therapies, such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and the polyagonists (GLP-1, GIP, and glucagon) currently being developed. This is mainly because of the way these medications affect body weight loss.

Table 1: Treatment Effects of Anti-Diabetic Drug Combination.

	Before intervention	After intervention	p-value*
ALT	94.5±9.1	68.01±7.6	<0.001
AST	86.05±9.0	75.2±3.2	<0.001
Triglyceride	249.04±29.3	174.6±42.1	<0.001
HBA1C	8.04±1.3	6.5±0.5	<0.001
TSH	13.7±1.9	11.0±1.4	<0.001
BMI (kg/m^2)	27.5±1.6	21.6±1.8	<0.001

*Significant value by paired sample t-test. [ALT: Alanine Transaminase, AST: Aspartate Aminotransferase, BMI: Body Mass Index, TSH: Thyroid Stimulating Hormone]

Fibroblast growth factor (FGF)19 and FGF21-based treatments, as well as SGLT2 inhibitors, appear to be potential targets for the treatment of NASH and type 2 diabetes. Due to short-term randomized trials, all of these medications have the limitation of having a limited impact on liver fibrosis.[19] Pioglitazone has been proven to alleviate the histological characteristics of NASH among anti-diabetic medications. The impact of more modern anti-diabetic medications, such as dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), on NAFLD/NASH have lately drawn more attention.[20]

Peroxisome proliferator-activated receptor agonists, sodium-dependent glucose cotransporter inhibitors, and glucagon-

like peptide-1 analogues have all been demonstrated to improve metabolic parameters and decrease hepatic lipid buildup and inflammation. But it is necessary to determine how these anti-diabetic medications precisely reverse NASH.[21] Pioglitazone emerges as a particularly compelling candidate among the spectrum of anti-diabetic medications due to its well-established and robust evidence supporting its potential role in treating Nonalcoholic Fatty Liver Disease (NAFLD). The empirical support garnered by pioglitazone underscores its efficacy in managing NAFLD, positioning it as a significant contender in the therapeutic landscape for this condition.[22] One noteworthy aspect is the discernible impact of pioglitazone on liver histology, particularly in individuals diagnosed with biopsy-proven Nonalcoholic Steatohepatitis (NASH). Studies and research endeavors have consistently demonstrated that pioglitazone has the capacity to improve liver histology in these individuals, thereby suggesting its ability to mitigate the inflammation and cellular damage characteristic of NASH. However, it is pertinent to acknowledge that despite pioglitazone's promising attributes, there are considerations that warrant attention. Notably, there may be associated adverse effects or limitations tied to its use, which should be weighed against its potential benefits. This comprehensive assessment is essential for making informed treatment decisions and ensuring the well-being of patients. Shifting focus, while it might still be early to definitively recommend the use of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) for the treatment of liver disease in NAFLD patients, one specific member of this class, liraglutide, has exhibited encouraging outcomes in this realm.[22]

When used alone or in combination with the effective statin therapy that is advised in T2DM, newer anti-diabetic medications (SPPARMs, GLP-1 RA, and SGLT2i) may significantly contribute to the amelioration of NAFLD/NASH, thereby lowering both liver-specific and cardiovascular morbidity.[23] Empagliflozin alone slows the progression of NASH and has anti-steatotic and anti-inflammatory effects, but when taken with linagliptin, it can effectively slow the progression of NASH and have better anti-fibrotic effects.[24] This study showed that the effect of combined empagliflozin and linagliptin drugs is more effective as compared to alone. It reduced the ALT and AST level along with triglycerides, sugar level as well as hypoglycemia.

Pioglitazone has the best evidence of potential efficacy among the currently available anti-diabetic medications, but there are also significant possible adverse effects, most notably peripheral edoema that might lead to weight gain, that need to be taken into account. However, further information is needed. Liraglutide is also encouraging.[25]

CONCLUSION:

The administration of the combined antidiabetic drugs empagliflozin (25 mg) and linagliptin (5 mg) demonstrated a secure and effective profile in mitigating the risk of Nonalcoholic Steatohepatitis (NASH) through a standardized dosage. This intervention yielded promising outcomes, including notable reductions in both ALT and AST levels, as well as a decrease in BMI, triglyceride levels, and HBA1C. Additionally, the treatment exhibited the potential to curtail the advancement of advanced liver disease NASH, underlining its relevance as a therapeutic strategy.

Remarkably, the utilization of these antidiabetic drugs also led to enhancements in fibrosis, with participants displaying improved fibrosis levels assessed as F1–F2 on transient elastography. Furthermore, the combined treatment exhibited a compelling impact on a key primary outcome, specifically lowering the risk of mortality linked to cardiovascular causes and reducing hospitalizations related to heart failure and kidney disease. These findings collectively highlight the multifaceted positive effects of the empagliflozin and linagliptin combination, positioning it as a promising avenue for addressing NASH and associated complications.

Authors Contribution:
Sana Abdul Razzak: Conception and design
Pervez Ashraf: Manuscript writing, data analysis, interpretation

REFERENCES:

1. Dufour J-F, Scherer R, Balp M-M, McKenna SJ, Janssens N, Lopez P, et al. The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors–A targeted literature review. Endocrine and Metabolic Science. 2021;3:100089.
2. Povsic M, Wong OY, Perry R, Bottomley J. A structured literature review of the epidemiology and disease burden of non-alcoholic steatohepatitis (NASH). Advances in therapy. 2019;36:1574-94.
3. Program TNE. How prevalent is NASH? 2019. Available from: https://www.the-nash-education-program.com/what-is-nash/how-prevalent-is-nash/.
4. Aldossari KK. The epidemiology and characteristics of patients with diabetes with or without NASH: a systematic review. African Health Sciences. 2023;23(2):509-18.
5. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. 2011;140(1):124-31.
6. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP reports. 2019;1(4):312-28.
7. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. 2002;35(2):373-9.
8. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. 2020;71(2):495-509.

9. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. 2019;42(8):1481-8.
10. Goossens N, Isgro G, Negro FJCDoSR. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. 2013(4).
11. Socha P, Horvath A, Vajro P, Dziechciarz P, Dhawan A, Szajewska HJJopg, et al. Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review. 2009;48(5):587-96.
12. Rakoski MO, Singal AG, Rogers MA, Conjeevaram HJAp, therapeutics. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. 2010;32(10):1211-21.
13. clinic M. Empagliflozin And Linagliptin (Oral Route) 2022. Available from: https://www.mayoclinic.org/drugs-supplements/empagliflozin-and-linagliptin-oral-route/precautions/drg-20137736?p=1.
14. Tetri BA. Nonalcoholic Fatty Liver Disease (NAFLD) & NASH: NIH; 2022. Available from: https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash.
15. Watada H, Yamauchi T, Yamamoto F, Taniguchi A, Yarush L, Heilmann C, et al. Safety and tolerability of empagliflozin and linagliptin combination therapy in patients with type 2 diabetes mellitus: a pooled analysis of data from five randomized, controlled clinical trials. 2020;19(9):1193-202.
16. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md). 2018;67(1):328-57.
17. Blond E, Disse E, Cuerq C, Drai J, Valette P-J, Laville M, et al. EASL–EASD–EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral? Diabetologia. 2017;60:1218-22.
18. Cusi K. A diabetologist's perspective of non-alcoholic steatohepatitis (NASH): Knowledge gaps and future directions. Liver International. 2020;40:82-8.
19. Smati S, Canivet CM, Boursier J, Cariou B. Anti-diabetic drugs and NASH: from current options to promising perspectives. Expert Opinion on Investigational Drugs. 2021;30(8):813-25.
20. Ranjbar G, Mikhailidis DP, Sahebkar A. Effects of newer antidiabetic drugs on nonalcoholic fatty liver and steatohepatitis: Think out of the box! Metabolism. 2019;101:154001.
21. Kothari S, Dhami-Shah H, Shah SR. Antidiabetic Drugs and Statins in Nonalcoholic Fatty Liver Disease. Journal of Clinical and Experimental Hepatology. 2019;9(6):723-30.
22. Kim KS, Lee BW. Beneficial effect of anti-diabetic drugs for nonalcoholic fatty liver disease. Clinical and molecular hepatology. 2020;26(4):430-43.
23. Athyros VG, Polyzos SA, Kountouras J, Katsiki N, Anagnostis P, Doumas M, et al. Non-alcoholic fatty liver disease treatment in patients with type 2 diabetes mellitus; new kids on the block. 2020;18(2):172-81.
24. Jojima T, Tomotsune T, Iijima T, Akimoto K, Suzuki K, Aso YJD, et al. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. 2016;8(1):1-11.
25. Iogna Prat L, Tsochatzis EAJH. The effect of antidiabetic medications on non-alcoholic fatty liver disease (NAFLD). 2018;17(2):219-29.

Original Article **Open Access**

Knowledge's and Practices of Cross Infection Control Protocols among Dental Health Care Professionals in Public Sector University of Karachi, Pakistan

Hina Shah, Sadaf Talha, Syed Mohsin Ahmed Rizvi, Marium Irshad, Aruba Fatima, Nazish Nisar

ABSTRACT

Objectives: 1. To assess the knowledge and practices of cross-infection control protocols among dental health care professionals (DHCP).

2.To compare the scores among different groups: junior and senior, male and female DHCPs, as well as between doctors and non-doctors.

Study design and setting: A cross-sectional study was conducted involving 112 DHCPs from a public sector university in Karachi, Pakistan.

Methodology: Participants were provided with self-administered questionnaires, consisting of closed-ended and multiple-choice questions, designed to evaluate their knowledge and practices concerning cross-infection control. The data was analyzed using SPSS version 26, with a significance level set at p=0.05 for comparison of scores.

Results: Data of 112 participants was analyzed. The male to female ratio was 3:5 with mean age of 25 years. 97.3% of the population believed aerosols as main cause of communicable diseases reported to be vaccinated for hepatitis B. The knowledge was good, and practices were adequate to ensure cross-infection control, but we found difference between the diploma holders and graduate/postgraduates and between graduate and postgraduates at p-value 0.05.

Conclusions: The results indicate showed the knowledge and practices to be adequate. Increased awareness and stringent adherence to PPE usage may have been influenced by a change in mindset following the recent pandemic. Though seminars and workshops should be arranged to provide them with updates. Also, vaccination against communicable diseases should be made mandatory for professional practice.

Keywords: Awareness, Comparative Study, Cross-Infection Control, Dental Health Care Professionals,

How to cite this Article:
Shah H, Talha S, Rizvi SMA, Irshad M, Fatima A, Nisar N. Knowledge's and Practices of Cross Infection Control Protocols among Dental Health Care Professionals in Public Sector University of Karachi, Pakistan. J Bahria Uni Med Dental Coll. 2023;13(4):286-90
DOI: https://doi.org/10.51985/JBUMDC2023242

Hina Shah *(Corresponding Author)*
Assistant Professor, Department of Community Dentistry
Jinnah Sindh Medical University
Email: hina.shah@jsmu.edu.pk

Sadaf Talha
Assistant Professor, Department of Orthodontics
Liaquat College of Medicine & Dentistry
Email: sadaf_taurus123@live.com

Syed Mohsin Ahmed Rizvi
Lecturer, Department of Oral Pathology
Jinnah Sindh Medical University
Email: mohsin.rizvi@jsmu.edu.pk

Marium Irshad
Final year Student BDS
Jinnah Sindh Medical University
Email: mariumirshad123@gmail.com

Aruba Fatima
Final year Student BDS
Jinnah Sindh Medical University
Email: aruba3fatima@gmail.com

Nazish Nisar
Final year Student BDS
Jinnah Sindh Medical University
Email: nazishnisarnh@gmail.com

Received: 29-08-2023
Accepted: 02-10-2023

INTRODUCTION:

Infectious diseases remain a significant threat to Pakistan's healthcare system, a situation exacerbated by the widespread hepatitis and HIV epidemic in the country.[1] It is estimated that approximately 12 million people in Pakistan are afflicted with Hepatitis B or C, with an annual increase of about 150,000 individuals.[2] In clinical environments, a myriad of microorganisms, including mycobacterium tuberculosis, streptococci, staphylococci, HBV, HCV, HIV, HSV, mumps, rubella, and other viral and bacterial agents, can be transmitted between patients and healthcare personnel. This transmission results in cross-infection via infected aerosols, blood, saliva, droplets, and contact with equipment contaminated with secretions.[3,4] Dental procedures are particularly associated with the risk of blood-borne diseases, as blood exposure can readily occur in dental clinical settings, thereby endangering dentists and their assistants.[5,6] The most common route of cross-infection in oral procedures is through intact skin or mucosa, resulting from sharp instruments or direct inoculation into wounds and abrasions on the skin.

Preventing cross-contamination is achievable by adhering to the universal precautions prescribed by the Centers for

Disease Control and Prevention (CDC) and the Occupational Safety and Health Administration (OSHA).[7] Additionally, healthcare facilities must establish and implement an exposure control plan (ECP), encompassing biohazard waste disposal.[8] It is imperative to prevent cross-infection in dental offices and schools during dental procedures, necessitating strict adherence to preventive and safety guidelines by all para-dental auxiliaries, especially when interacting with patients.[9]

Consequently, it is vital for Dental Health Care Professionals (DHCPs) to adhere to comprehensive safety measures, including wearing personal protective equipment (PPE) such as gowns, gloves, masks, and eyewear. DHCPs must also utilize high-speed suction systems when operating high and low-speed rotary tools. Gloves and gowns should be worn upon entering and exiting the patient's room, followed by immediate hand hygiene.7

Proactive prevention and the implementation of necessary measures are fundamental to mitigating the risks of cross-contamination and cross-infection. Therefore, this study aims to compare the awareness and practice of cross-infection control protocols among DHCPs at a public sector university in Karachi, Pakistan. Specifically, the study assessed the awareness and practice of cross-infection control protocols among DHCPs and compares these aspects among junior and senior, male and female DHCPs, as well as between doctors and dental hygienist and assistants. A lack of awareness and practice regarding infection control protocols can lead to an increased risk of transmission of infections. Previous studies have shown a lack of awareness and practice among DHCPs in various parts of the world.[5,6,8] However, there is limited data available on the awareness and practice of cross-infection control protocols among DHCPs in Pakistan, particularly in Karachi.[10-12] This study aims to fill this gap by providing valuable insights into the current status of awareness and practice of cross-infection control protocols among DHCPs in a public sector university in Karachi, Pakistan. Ultimately, the findings of this study will help in identifying areas that need improvement and in developing targeted interventions to enhance the awareness and practice of cross-infection control protocols among DHCPs in Pakistan.

METHODOLOGY:

This research was approved by an institutional review board of Jinnah Sindh Medical University (Reference # JSMU/IRB/2022/602. A Cross-sectional study was conducted to assess the awareness and practice of cross-infection control protocols among dental health care professionals (DHCPs) in the public sector University of Karachi, Pakistan. The study was conducted from 1st June to October 2022. All dentists, professors, associate professors, assistant professors, lecturers, demonstrators, postgraduate trainees, fellows, house officers, hygienists, therapists, prosthetists, technicians, and dental assistants were included in the study.

A non-random convenience sampling technique was employed to recruit participants. For sample size, select statistics online calculator was used. Considering that 93.5% of participants followed appropriate infection control measures during dental procedures as reported by Shenoy et al., keeping the confidence level of 95%, a margin of error of 5%, a minimum sample size of 94 was calculated.[13] Data was gathered from 112 DHCPs affiliated with JSMU. Informed consent was obtained from each participant before recruitment.

A self-administered structured questionnaire was designed and used to collect data from the DHCPs. The questionnaire consisted of closed-ended questions regarding practitioners' vaccination status, patient history-taking habits, and hygiene habits during practice, sterilization, and irrigation type preferences. It consisted of multiple-choice questions and the participants were asked to choose the best option.(annexure 1)

Undergraduate medical and dental students, foreign dentists, those with no clinical experience either teaching or non-teaching, and those who did not provide consent were excluded from the study. No personal details, including complete names, residential addresses, or phone numbers, were recorded or gathered. The principal researcher and the co-researcher had unrestricted access to the data at all moments. This guaranteed the integrity of their anonymity and confidentiality for the entire duration of the study.

All the data was entered and analyzed into the Social Package of Statistical Sciences SPSS version 26. Percentages and frequencies are calculated to assess the awareness and practice of that knowledge amongst Dental Health Care Practitioners (DHCPs). Additionally, a comparison was done between the male and female, senior and junior DHCP, and doctors and other dental health care providers using ANOVA and post hoc analysis was used to find out difference in answers for the knowledge and practical use of cross-infection protocols. For all comparative analyses, the level of significance is at p=0.05. This helps assess the impact of formal education on the practical use of cross-infection measures.

RESULTS:

A total of 112 dental health care professionals participated in the study with a mean age of 25 years, and a male-female ratio of 3:5. The overall mean experience of working in hospital-based setting was of 6 years. Out of our 112 participants, n=73 (65%) DHCPs reported having been vaccinated against HBV. 61.6% of the sample size reported personally checking for vaccination reports of patients while the rest didn't check for any vaccination reports. When asked about the type of diseases that can be transmitted during a dental checkup, 97.3% of the population pointed out airborne diseases as the culprit. when inquired how many times the dental units were cleaned in this public

hospital, n= 90(80.4%) of the population reported only once daily, 5.4% reported thrice daily, and 14. 3% of the population reported the units to be cleaned after every patient. The participant's responses to the following cross-infection control precautions are mentioned in table 1. While Table 2 shows that only 61.6%(n=69) of the team checking for reports of patients treated for communicable diseases or with comorbid that may affect treatment. When asked about the their own vaccination they reported highest for Hepatitis B(n=45,40.2%) and only 4.5%(n=5) said they were not vaccinated. ANOVA was used to find out the differences between the approached and knowledge between the participants. None of the findings were significant. Though on post-hoc analysis with Scheff`s test the findings for Gloves worn during treatment, Mask worn during treatment, Coat during treatment, Sterile instrument, Hand wash after, Critical instrument, Semi critical instrument, Disease check, Report vaccination, Unit Cleaning frequently were found to be significant up to p-value of 0.05(Table 3).

Table 1. Responses to cross-infection control precautions

Practices	Every time	Sometimes	Never
Use gloves during treatment	94.6% (106)	4.5%(5)	0.9%(1)
Use mask during treatment	93.8% (105)	6.3% (7)	-
Use sterilized instruments	98.2% (110)	1.8%(2)	-
Use white coat during	75% (84)	20.5% (23)	4.5%(5)

Item	**Answer**	**N**	**Percentage**
Check for reports of the patient	Yes	69	61.6%
	No	43	38.4%
Vaccinated against	Hepatitis B	45	40.2%
	Tuberculosis	10	8.9%
	Tetanus & BCG	24	21.4%
	None	5	4.6%
	All the above	28	25%

DISCUSSION:

A patient trusts the healthcare personnel working on them to bring them out of pain and solve the dental problem they came with rather than give them an infection through irresponsible practice of cross-infection control measures. The Pakistan dental curriculum equips its students with all the important measures for cross-infection control to not only protect themselves but also their patients. This study shows that while a majority of dental healthcare practitioners do follow universal precautions, there is a lot of room for improvement. Using sterilized instruments every time is very basic- the practice should be strictly followed by all. washing hands before treatment needs more emphasis. Disinfecting the dental unit after every patient should not just be ideal but should be a standard. This study however has unveiled how PPE practices have changed from previous years.

Due to limitation of resources and facilities, developing countries lack the state-of-the-art equipment available to practice Dentistry. Most hospitals and clinical settings lack

Table 3: Difference in knowledge and practices of Dental Health Care Providers (Scheff`s analysis)

Dependent Variable	**Dental Qualification**		**Mean Difference (I-J)**	**Std. Error**	**Sig.**
	I	**J**			
Gloves worn during treatment	Diploma holder/Certified	Post graduation/doctorate	.44444*	.12688	.009
	Graduation	Post graduation/doctorate	.42294*	.08789	.000
Mask worn during treatment	Diploma holder/Certified	Post graduation/doctorate	.44444*	.10675	.001
	Graduation	Post graduation/doctorate	.42294*	.07395	.000
Coat worn during treatment	Diploma holder/Certified	Graduation	-.80645*	.19663	.001
Use of Sterile instruments	Diploma holder/Certified	Post graduation/doctorate	.22222*	.06048	.005
	Graduation	Post graduation/doctorate	.22222*	.04190	.000
Hand wash after treatment	Graduation	Post graduation/doctorate	.36918*	.11696	.023
Disinfectant used for Critical instrument	Diploma holder/Certified	Post graduation/doctorate	1.26984*	.27950	.000
	Graduation	Post graduation/doctorate	1.18996*	.19361	.000
Disinfectant used for Semi critical instrument	Graduation	Post graduation/doctorate	.69534*	.15781	.000
During history asking about Diseases	Diploma holder/Certified	Undergraduate	-.42857*	.08694	.000
		Graduation	-.42857*	.04938	.000
		Post graduation/doctorate	-.42857*	.06349	.000
Patient`s report for vaccination	Graduation	Post graduation/doctorate	.57706*	.16776	.010
Relevant person for cleaning Unit.	Diploma holder/Certified	Undergraduate	1.71429*	.43115	.002
		Graduation	1.43472*	.24488	.000
		Post graduation/doctorate	1.71429*	.31487	.000

infection control policies due to a lack of understanding of the risks or a lack of adequately trained staff. The Centre for Disease Control (CDC) published guidelines for infection control in dental settings in 2003.[2,7] The major goal of OSHA guidelines is to create a safe working environment for dentists, DHCPs, and their patients, as well as to prevent the spread of dangerous infections and nosocomial illnesses. According to the CDC's guiding principles, face masks and gloves must be used during all dental treatments on every patient, and the masks and gloves must be changed after each procedure. Disinfection of clothes before reusing them has also been very talked about. Additionally, after performing chair-side dental treatments, hands must be thoroughly cleaned with an antiseptic solution which is a common technique for reducing the risk of illness and spreading it.[7]

As dentists and their assistants are at a higher risk of contracting the viruses, if infection control principles are not followed, they can contribute to the spread of infection and disease to dental patients. Infection control can be achieved by following conventional recommendations. Unfortunately, evidence suggests that DHCPs have little knowledge, unfavorable attitudes, and poor practices when it comes to infection control.[14] Exposure to infections can be avoided by using universal precautions. Pre-operative self-vaccination and post-operative hygiene and disinfection play a key role in avoiding infections.[5]

We conducted a pilot study to find out the reliability and validity of the questionnaire on sample of 10 participants from all 4 categories (n=2 each) and found it to have good face validity and Cronbach's Alpha of 0.7. After that the final data collection was started. We included the results from the pilot study into the final data.

In current study, the out of the 112 sample, 65% (n=73) reported to being vaccinated against HBV and 97.3% of the respondents were aware of what infections could they contract from patients and vice versa. On comparing this to the available literature from Egypt, Saudi Arabia, India and Pakistan we found that either they had included dental assistants or dental students in the sample leaving the other dental health care providers.[11,15-17] Only one study from India covered everyone from dental health care team.[18] The questions from the mentioned were different from ours. But mostly covered the knowledge and practice part both. When they were asked if they know about infection control facilities available to them, 60% knew about them. Around 67.6% used protective equipment during treatment, when compared to our results we found that 90% use personal protective equipment including protective eye wear, mask, gloves and lab coat.

The mean knowledge score between the dental practitioners and the dental assistants in the Indian study was higher for dental assistants (Mean Score=5.79) in comparison to dentist (Mean Score=2.03).[16] This difference in knowledge and practices in our study was analyzed through Post-hoc (Schaff` test). Mostly there was a significant difference specially between assistants/hygienist (certified/diploma holders) and postgraduates (faculty and postgraduate trainees) (Table 3) at p-value 0.05. Few of the practices showed difference in practices between graduate and postgraduate: gloves worn during treatment, mask worn during treatment, use of sterile instruments, hand wash after treatment, disinfectant used for Critical instrument, disinfectant used for semi critical instrument, patient`s report for vaccination which are significant at p-value 0.05.Similarly, few of the practices showed significant differences at p-value 0.05 between undergraduate and diploma health care providers including during history asking about diseases and relevant person for cleaning Unit.

It is very important that the reports of the patient`s reporting with history of undergoing treatment for communicable diseases or other disease that may alter the dental treatment, should be checked. This important detail was not covered in the above-mentioned study.[16] While our results showed that 61.6% of the personnels checked for reports and secondly when they were asked for what diseases they were vaccinated, they reported that only 40% were vaccinated against hepatitis B which is low implying that adequateness of the knowledge and practices were as per the universal precautions for cross-infection control which may have can be the result of the covid 19 pandemic which increased the general awareness of PPE.[19,20] Other important factors specially vaccination status of the health care provider is necessary for the safety of the practitioner but also of the patients.

CONCLUSION:

The overall knowledge and practices of staff and dentist working at Sindh Institute of Oral Health sciences are satisfactory and concrete measures are in place to decrease the chances of cross infection to patients, attendants, janitorial and dental staff as well as dentists. The findings show that there is difference between the Dental staff and Dentists knowledge and practices for cross-infection control. It is suggested to achieve cross-infection control, regular training through workshops or seminars and support of the faculty and staff both auxiliaries and janitorial is necessary to pre-prepare the staff to deal with future endemics/pandemics as faced during COVID-19 time recently. This will support cross-infection control.

Authors Contribution:
Hina Shah: Conceptualized the study, acquisition, collection, statistical analysis & interpretation data manuscript writing
Sadaf Talha: Contributed to the study design, reviewed and approved the manuscript
Syed Mohsin Ahmed Rizvi: Contributed in data collection and edited the manuscript
Marium Irshad: Contributed in data collection
Aruba Fatima: Contributed in data collection
Nazish Nisar: Contributed in data collection

REFERENCES :

1. Ali SA, Donahue RM, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. International journal of infectious diseases. 2009;13(1):9-19. doi: 10.1016/j.ijid.2008.06.019.
2. Prevention and control of hepatitis [Internet]. World Health Organization. 2021. Available from: https://www.emro.who.int/pak/programmes/prevention-a-control-of-hepatitis.html.
3. Elagib MF, Baldo SM, Tawfig A, Alqarni MA, Ghandour I, Idris AM. Knowledge, attitude, and practice regarding infection control measures among dental students during COVID-19 pandemic. Archives of environmental & occupational health. 2022;77(6):455-67. doi:10.1080/19338244.2021.1931796.
4. Ibrahim NK, Alwafi HA, Sangoof SO, Turkistani AK, Alattas BM. Cross-infection and infection control in dentistry: Knowledge, attitude and practice of patients attended dental clinics in King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Journal of infection and Public Health. 2017;10(4):438-45.
5. Broussard IM, Kahwaji CI. Universal Precautions. [Updated 2023 Jul 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470223/
6. OSHA Hazard Communication Standard and OSHA Guidelines, (2022). Available from: https://www.osha.gov/hazcom.
7. Cuming RG, Rocco TS, McEachern AG. Improving compliance with occupational safety and health administration standards. AORN journal. 2008;87(2):347-60.
8. Khan N, Batool SM, Ali M, Ahmed M, Noor A, Afzal J. Knowledge, Awareness & Practice about Cross Contamination Control among the Students of Dentistry. Pakistan Journal of Medical & Health Sciences. 2022;16(05):176-8.doi: https://doi.org/10.53350/pjmhs22165176
9. Mahasneh AM, Alakhras M, Khabour OF, Al-Sa'di AG, Al-Mousa DS. Practices of infection control among dental care providers: a cross sectional study. Clinical, Cosmetic and Investigational Dentistry. 2020:281-9.doi:10.2147/ CCIDE. S261171
10. Kumar C, Khalid M, Bibi T. Awareness and behavior of dental students towards infection control measures in Karachi, Pakistan. Journal of Bahria University Medical and Dental College. 2018;8(3):142-5.doi: https://doi.org/10.51985/JBUMDC2018035
11. Javaid M, Sahu EH, Malik A, Khan N, Noor A, Shaukat MS. Practice of personal protective equipment among dental surgery assistants: survey from a public sector hospital. Journal of the Dow University of Health Sciences (JDUHS). 2020;14(2):66-71.doi: https://doi.org/10.36570/ jduhs. 2020. 2.936.
12. Gawish A, Khalifa A. InfectIon control PractIces among grouP of Dental HealtH care ProvIDers. Egyptian Dental Journal. 2016;62(1-January (Oral Surgery)):971-6. doi:10.21608/edj.2016.95231
13. Shenoy N, Ballal V, Rani U, Kotian H, Lakshmi V. Assessment of knowledge, attitude and practices among dental practitioners on methods of infection control while carrying out dental procedures during novel coronavirus (COVID-19) pandemic. Pan African Medical Journal. 2021;39(1). doi:10.11604/pamj.2021.39.265.29003
14. Harrel SK, Barnes JB, Rivera-Hidalgo F. Aerosol and splatter contamination from the operative site during ultrasonic scaling.J Am Dent Assoc.1998;129(9):1241-9. doi:10.14219/jada.archive.1998.0421.
15. Al-Hindawy GE, Attia NM, Hegazy SA. Evaluation of Knowledge, Attitude, and Practice of Infection Control principles Among A Sample of Egyptian Dental Students. Mansoura J of Dentistry. 2021;8(29):10-6.doi: 10.21608/ mjd.2021.199843
16. ALOsaimi MM, Almeslet AS, ALWisali QM. Knowledge, Attitude, and Practice of Infection Control among Dental Healthcare Personnel: The Updated Guidelines for COVID-19 in Dental Settings. The Journal of Contemporary Dental Practice. 2022;23(11):1151.doi: 10.5005/jp-journals-10024-3430.
17. Ravichandran RK, Jain J, Ananda S, Jaduram B, Gunasekaran S. Knowledge, attitude and practices regarding hepatitis B and infection control among clinical dental students. Int J Applied Dent Sci. 2019;5(3):42-6.
18. Sachdeva A, Sharma A, Bhateja S, Arora G. Knowledge, attitudes, and practices regarding sterilization protocol among undergraduate dental students in Faridabad City: A questionnaire-based study. Journal of Indian Academy of Oral Medicine and Radiology. 2019;31(1):4-10. Doi: https://doi.org/10.4103/jiaomr.jiaomr_186_18
19. Bizzoca ME, Campisi G, Lo Muzio L. Covid-19 pandemic: What changes for dentists and oral medicine experts? A narrative review and novel approaches to infection containment. Int J Environ Res Public Health. 2020 May 27;17(11):3793. doi: 10.3390/ijerph17113793.
20. Loch C, Kuan IB, Elsalem L, Schwass D, Brunton PA, Jum'ah A. COVID-19 and dental clinical practice: Students and clinical staff perceptions of health risks and educational impact. J Dent Ed): 44-52.doi(1):44-52.doi: https://doi.org/10.1002/jdd.12402.

Original Article **Open Access**

Mandibular Asymmetry in Orthodontic Patients with Different Malocclusion Patterns an Orthopantomographic Evaluation

Omair Majeed, Tabassum Ahsan Qadeer, Maria Habib, Ayesha Ashraf

ABSTRACT:

Objectives: To investigate the variation in mandibular asymmetry on right and left sides for different malocclusions.

Study design and setting: It was a cross sectional study carried out in Orthodontic Department at Bahria University Dental College. OPG's of 171 orthodontic patients were collected. The sample was divided into class I, II and III malocclusions.

Methodology: The OPG was traced for condylar and ramal heights for both right and left sides. From these readings, the asymmetry index (AI) was calculated for each side. The significance of height variations between the right and left sides, for each malocclusion was calculated using independent sample t-test. Pearson correlation was used to find the association of asymmetry between the two sides when comparing each malocclusion with the other. One-way ANOVA was used to find the significance of differences in asymmetry index of both sides between different malocclusions.

Results: The ramal heights were significantly different for each malocclusion with p values of 0.00 and 0.02 for right and left side, the p value of the variations in condylar heights was however 0.66 and 0.12 for the two sides. There was a strong positive correlation of the condylar and ramal height on both sides between all three malocclusions. The p value for condylar AI was 0.97 and 0.15 for ramal AI.

Conclusion: The ramus height showed a significant variation in asymmetry while the asymmetry index variations were insignificant between different malocclusion groups.

Keywords: Asymmetry, Asymmetry index, Malocclusion, Condylar height, Ramal height

How to cite this Article:
Majeed O, Qadeer TA, Habib M, Ashraf A. Mandibular Asymmetry in Orthodontic Patients with Different Malocclusion Patterns an Orthopantomographic Evaluation. J Bahria Uni Med Dental Coll. 2023;13(4):291-5 DOI: https://doi.org/10.51985/JBUMDC202162

INTRODUCTION:

Symmetry or proportion refers to equality and resemblance in shape, size and location of facial landmarks on either sides of the median sagittal plane.[1] The facial structures of humans play an important role in regard to social relationships. A balanced and symmetric facial appearance plays a major role in influencing human attractiveness and desirability. However, perfect symmetry is a myth and does not exist. Many faces that appear symmetric and proportional on clinical examination show varying degrees of craniofacial asymmetry on cephalometric studies.[2]

Asymmetry becomes significant when it influences esthetics or social appearance of an individual.[3] Mild asymmetry of the orofacial region is a common finding in a general population however the incidence of clinically apparent facial asymmetry has been reported to be 34–38.6% in patients with dentofacial deformities and 23% in the orthodontic population. Facial asymmetry is more frequently found in patients of skeletal Class III, with an incidence of 40– 80%, possibly due to excessive mandibular growth in the case of mandibular prognathism and can be a risk factor for unbalanced development on both sides of the mandible. Therefore, thorough clinical and radiological evaluation for facial asymmetry is particularly important in skeletal Class III patients.[4]

Asymmetry of the mandible is a craniofacial feature occurring in all types of sagittal malocclusion.[5] It is significant because of its direct effect on facial appearance both in terms of esthetics as well as function.[1,6] Proffit[7] reported that 75% of facial asymmetry patients showed chin deviation, 36% had middle-third asymmetry while asymmetry of the upper face was seen in only 5% patients.[3,8]

The etiology of mandibular asymmetry can be attributed to environmental, genetic or functional factors.[9] It is important

Omair Majeed: *(Corresponding Author)*
Senior Lecturer, Department of Orthodontics
Bahria University Health Sciences, Karachi
Email: dromairis@hotmail.com

Tabassum Ahsan Qadeer:
Professor, Department of Orthodontics
Bahria University Health Sciences, Karachi
Email: ahsan.tab@gmail.com

Maria Habib:
Assistant Professor, Department of Orthodontics
Bahria University Health Sciences, Karachi
Email: mrsfurrukh@gmail.com

Ayesha Ashraf:
Lecturer, Department of Orthodontics
Bahria University Health Sciences, Karachi
Email: ayeshaashrafkhan@gmail.com

Received: 14-09-2021
Accepted: 12-09-2023

to determine the aetiological factor and to identify the site of the asymmetry in order to achieve a balanced and harmonious facial appearance following orthodontic or surgical treatment. Asymmetry may originate from morphological disorders including abnormal growth, tumors, trauma, condylar hyperplasia, hemi- mandibular hypertrophy and elongation as well as hyperplasia of the coronoid process. Functional causes such as muscle dysfunctions, bruxism and temporomandibular joint dysfunction may also cause mandibular asymmetry. Malocclusions also have a significant effect on mandibular condyle morphology.[2] One of the main determinants of mandibular growth are the primary and secondary cartilages of the mandible that appear at different times of growth. Growth of the mandibular condyle contributes not only to increased mandible size, but also to anteroinferior displacement (transposition) of the mandible. Condylar growth direction is closely related to the displacement (transposition) direction of the mandible and vertical jaw deviations. The condylar cartilage is one such cartilage that has the highest growth potential and aberrations in the growth of this cartilage due to trauma, congenital diseases or infection can lead to condylar asymmetries rendering them the most common reason for mandibulofacial asymmetries.[10]

Although correlation of mandibular asymmetry and Angle's malocclusion has been studied, however we failed to find local studies on it. Therefore the aim of this study was to investigate the relationship between the occlusal patterns and mandibular asymmetry in our population.

METHODOLOGY:

Ethical approval of the study was obtained from ERC of BUMDC with ref. no. ERC24/2021. It was a retrospective cross sectional study, conducted on the records of patients attending the Orthodontic OPD at BUMDC, who were between 18-30 years of age.

The sample size of 171 subjects was determined by using software G Power version 3.1.9.2 by taking 5% margin of error and 95% confidence interval. The sample was divided into three subgroups according to the malocclusion type. The number of subjects in each subgroup was 58 for Class I, 56 for class II and 57 for class III.

The inclusion criteria was dental class I II and III patients who did not present with any anterior or posterior cross bites or mandibular deviations during opening and closure. Patients who had a history of orthodontic treatment or occlusal and TMJ trauma or TMJ disorders were excluded from the study.

Care was taken in selection of radiographs and only clear ones that captured the entire mandible and presented with no artifacts were used. Panoramic radiographs were traced on an acetate paper, by a single calibrated examiner for all the patients, using a digital caliper with 0.01mm sensitivity. Figure 1 shows the method given by Habets et al who developed a method to quantify condylar asymmetry on panoramic radiographs using linear measurements of both condyles and ramii and comparing the difference between the right and left condylar and ramal heights.[11,12,13] The readings were taken for both the right and left sides. A line connecting the most lateral point of the condyle (O1) and the ascending ramus (O2) was drawn and mentioned as 'A'. Ramus height was the distance between the points O1 and O2, and called 'RH'. Line 'B' was drawn perpendicular to line 'A', touching the most superior part of the condyle. The vertical distance from this line till O1 was measured and named the condylar height, 'CH'. To reduce intra operator bias, 5 cases were randomly retraced to calculate the readings, the Kappa Statistics was found to be 0.8 indicating good agreement.

Asymmetry indices were then calculated for both the condyle (Condylar height right and left) and ramus (Ramus height right and left) using the following formula:

$$\text{Assymetry Index (AI)} = \frac{\text{Right} - \text{Left}}{\text{Right} + \text{Left}} \times 100$$

Statistical analysis was performed using SPSS version 23.0. All continuous variables were calculated as Mean± SD. Normality of data was checked by using Shapiro-Wilk test. Data was found to be Normal (Symmetric). Inferential statistics was performed to find out the height differences between the right and left sides for each malocclusion using independent sample t-test. Pearson correlation was used to find the association of asymmetry between the two sides when comparing each malocclusion with the other. One-way ANOVA was used to find the significance of differences in asymmetry index of both sides between different malocclusions. A p-value = 0.05 considered to be statistically significant.

RESULTS:

Table 1 shows the values of condylar and ramal height with comparison of each side, between different malocclusions, it was found to be statistically insignificant. The condylar height showed minimal difference between different malocclusions whereas the ramal height was most increased in the sample with class III malocclusions.

Pearson correlation showed significant associations in condylar and ramal heights between different malocclusions as shown in Table 2.

DISCUSSION:

There is a state of equilibrium between the two sides of the face in shape, size and form of the structures, however there is usually a dimensional difference between the two sides.[14] Mandibular asymmetry has important esthetic implications due to its direct effect on facial appearance. Various methods have been used to assess facial asymmetry including frontal cephalograms, postero-anterior radiographs, panoramic views, submentovertex views, CT, MRI as well as CBCT.[15,16]

Table 1: Comparison of Condylar and Ramal height values in mm for different groups

	Group	N	Mean ± SD	Min	Max	p value
Condyle	Class I	58	Rt = 8 ± 2.5	7.6	8.9	0.13
			lft = 7.6 ± 2.3	6.9	8.2	
	Class II	56	Rt = 7.9 ± 2.3	7.2	8.5	0.11
			lft = 7 ± 2.3	6.5	7.8	
	Class III	57	Rt = 8 ± 2.5	7.5	8.8	0.89
			lft = 8 ± 2.5	7.4	8.8	
Ramus	Class I	58	Rt = 42.5 ± 5	41.2	43.9	0.39
			lft = 43 ± 6	41.8	45	
	Class II	56	Rt = 43.6 ± 5.4	42.2	45.1	0.51
			lft = 44 ± 5.9	42.7	45.9	
	Class III	57	Rt = 47 ± 6.2	45.3	48.6	0.64
			lft = 46.5 ± 6	44.8	48.1	

p<0.05, SD= Standard Deviation, p value calculated using independent sample t-test

Table 2: Association between right and left side when comparing different malocclusions

	Class I and II		class I and III		class II and III	
	r-value	p- value	r-value	p- value	r-value	p- value
Condyle	0.4*	0.00*	0.3*	0.00*	0.3*	0.00*
Ramus	0.7*	0.00*	0.8*	0.00*	0.79*	0.00*

Data presented as correlation 'r' , p-value
correlation is significant at <0.05 level
calculated using Pearson Correlation

Table 3: Comparison of Asymmetry Index values in % for Condyle and Ramus between different groupS

CAI				
	Mean ± SD	**Min**	**Max**	**p value**
Class I	4.74 ± 16.7	-25	45	0.97
Class II	5.02 ± 17.4	-31	51.5	
Class III	4.36 ±16.07	-33	48.1	
RAI				
	Mean ± SD	**Min**	**Max**	**p value**
Class I	-0.92 ± 4.6	-11.5	8.7	0.15
Class II	-0.74 ± 5.1	-11.3	9.09	
Class III	0.56 ± 3.5	-7.5	10.1	

P<0.05 p value calculated using One-way ANOVA

Orthopantomograms however are the most commonly used imaging technique because it is possible to image the dentition, joints and the entire lower jaw in a single low radiation dose exposure making them a routine diagnostic investigations prior to commencement of orthodontic treatment.

Computed tomography is more accurate and reliable but the cost and increased radiation dosage does not make it a viable option for the majority of the population. Radiographic (OPG) measurements do have the disadvantage of distortion due to magnifications and the methodology used, but studies have been supportive in their use due to advantages like a low cost, relatively low levels of radiation exposure and in third world countries they are also readily available for retrospective studies.[2,9] It has also been suggested that with correct methodology and accurate patient positioning, vertical and angular measurements can be accurately calculated and can be believed to be reliable too.[17] Also the differences between the two sides would likely have the same magnification errors so comparative studies can be adequately performed. Studies have also shown that if the head position is stabilized, the vertical measurements are accurately reproducible.[4]

Habets technique is quite popular for calculation of mandibular symmetry in studies done on radiographs. He reported that if the head position changes by 1cm there would be a 6% change in the vertical dimension.[11,18] The formula for calculating the asymmetry index was developed in 1988 and it gives a 3% index rate from a 1 cm head shift, anything more suggests mandibular asymmetry. In our study the mean condylar asymmetry index was >3% for all malocclusions. This was in accordance to many studies including those of Saglam[19] and Miller[20] who calculated the AI in different malocclusion and found the values in the entire sample to be >3%.

Our study showed no significant variation of the AI values of condyle or ramus, between the three malocclusion groups. Thiesen et al[21] in their study showed that little difference was found, when comparing the same intensities of asymmetry in the different sagittal jaw relationships. This was also similar to the study of Kurt et al[22] who compared the mandibular asymmetry between class II and normal occlusion and did not find any statistical difference in the values between the two groups. A study conducted by Al Taki et al[23] however was the only study that we found which showed a statistically significant condylar asymmetry in class II group that they compared with class I malocclusion. Our sample showed that despite there being no significant variation of condylar AI between different malocclusions, the value shown by the class II sample was the highest. Along with that between the ramus and condylar asymmetry index, only the condylar showed a higher value for class II malocclusion similar to the results of Akin et al.[16] The AI of ramal heights was found to be highest in class III malocclusion in our study, despite having minimum variations.

When comparing the two sides of the mandible, some studies have shown the right side to be dominant or greater in certain dimensions, while some studies show that the larger readings were observed on the left side[2]. For our study we did not find any such relationship with both sides showing random greater and smaller readings with the differences being statistically insignificant as shown in Table 1.

While using Habets method for asymmetry calculation, it is recommended that AI values of >3% is taken into consideration. Our study found the CAI in all the malocclusions to be above 3%, however the RAI value was below that. This is in accordance to the study by Al TaKi et al[23] who found the RAI to be below the benchmark whereas the CAI was more than the prescribed 3%. Another study by Syeda and Roohi showed that CAI in normal occlusion and class II Div I malocclusion (males and females) were found above 3% indicating the presence of asymmetry.[24] Their CAI values, in contrast to many other studies were however much higher, being 9.13, 14.9 and 4.55 for class I II and III, as compared to our sample which was 4.74, 5.02 and 4.36 for the three malocclusion groups given in Table 3. Miller and Bodner, who compared the condylar asymmetry of class I and III, found the values to be 4.42% and 4.14%.[25] The reason that best explains this contrast in results could be the normal variation for different populations, as there was no major difference in the inclusion criteria's of these studies from our study. The age group of the sample by Al Taki et al was 19-28 years while ours was 18 years and above, so late growth resulting in asymmetry can be ruled out to major extent.[23] Convenience sampling was utilized for most studies from the orthodontic records of the patients visiting the OPD. A cohort sample in future studies can may help throw better light on this variation.

Limitations of our study included not dividing the class II sample into division 1 and 2.

CONCLUSION:

Our study showed that there was no significant variation in the mandibular asymmetry between the two sides for any type of malocclusion. The ramus height showed a significant variation in asymmetry between different malocclusions.

Authors Contribution:
Omair Majeed: FRC, ERC, Data compilation, Introduction writing
Tabassum Ahsan Qadeer: Writing Results, discussion and conclusion, Table making
Maria Habib: Data collection
Ayesha Ashraf: Data collection

REFERENCES;

1. Sezgin OS; Celenk P; Arici S. Mandibular Asymmetry in Different Occlusion Patterns. A Radiological Evaluation. Angle Orthod. 2007; 77(5):803-7. (DOI: 10.2319/092506-392)
2. Alkis HT, Bilge OM. Retrospective evaluation of mandibular asymmetry with panoramic radiography in Angle malocclusion samples. Med J SDU 2019;26(2):151-58. (DOI: 10.4103/njcp.njcp_597_18)
3. Mishra H, Shivaprakash G, Maurya RK. Assessment of Facial Asymmetry in Various Malocclusion: A Comparative Analysis. The Journal of Indian Orthodontic Society, October-December 2014;48(4):537-545. (https://doi.org/10.5005/jp-journals-10021-13120
4. Kim SJ, Baik HS, Hwang CJ and Yu HS. Diagnosis and evaluation of skeletal Class III patients with facial asymmetry for Orthognathic surgery using three-dimensional computed tomography. Semin Orthod. 2015;21(5):274-82. (https://doi.org/10.1053/j.sodo.2015.07.004)
5. Evangelista K, Teodoro AB, Bianchi J, Cevidanes LHS, Ruellas ACO, Silva MAG, Neto JV. Prevalence of mandibular asymmetry in different skeletal sagittal patterns: A systematic review.. Angle Orthodontist, Vol 92, No 1, 2022. (DOI: 10.2319/040921-292.1)
6. Sodawala J, Shekar SE, Mathew S. Evaluation of condylar asymmetry in different skeletal patterns in post adolescents. Int J Oral Care Res. 2014;2(3):1-6.
7. Severt TR, Proffit WR. The prevalence of facial asymmetry in the dentofacial deformities population at the University of North Carolina. Int J Adult Orthodon Orthognath Surg. 1997;12:171-6
8. Choi H, Kim B, Kim J, Huh J and Park K. Three-dimensional computed tomography evaluation of craniofacial characteristics according to lateral deviation of chin. CHOI et al. Maxillofacial Plastic and Reconstructive Surgery (2019) 41:57. (https://doi.org/10.1186/s40902-019-0241-1)
9. Bolat E, Alkis HT. Condylar and ramal vertical asymmetry in patients with different vertical skeletal patterns.Australasian Orthodontic Journal Volume 37 No. 1 May 2021. (DOI: https://doi.org/10.21307/aoj-2021-009)
10. Mizoguchi I *, Toriya N, Nakao Y. Growth of the mandible and biological characteristics of the mandibular condylar cartilage. Jpn Dent Sci Rev. 2013; 49:139-50. (https://doi.org/10.1016/j.jdsr.2013.07.004)
11. Habets LL, Bezuur JN, Naeiji M, Hansson TL. The Orthopantomogram, an aid in diagnosis of temporomandibular joint problems. II. The vertical symmetry. J Oral Rehabil. 1988;15:465–71 (https://doi.org/10.1111/j.1365-2842.1988.tb00182.x)
12. Celik S, Celikoglu M, Buyuk SK, Sekerci AE. Mandibular vertical asymmetry in adult orthodontic patients with different vertical growth patterns: A cone beam computed tomography study. Angle Orthodontist, Vol 86, No 2, 2016. (DOI: 10.2319/030515-135.1)
13. Mendoza, Luz & Bellot-Arcis, Carlos & Montiel-Company, Jose & García-Sanz, Verónica & Almerich-Silla, Jose & Paredes, Vanessa. (2018). Linear and Volumetric Mandibular Asymmetries in Adult Patients With Different Skeletal Classes and Vertical Patterns: A Cone-Beam Computed Tomography Study. Scientific Reports. 8. 10.1038/s41598-018-30270-7. (DOI:10.1038/s41598-018-30270-7)
14. Akin M, Ileri Z, Polat O, Basciftci FA. Evaluation of mandibular asymmetry in class II subdivision malocclusion. Selcuk Dent J. 2015; 2: 43-50
15. Khan EB, Rafi T, Tauheed S, Jafri AR, and Ali N. Assessment of the Mandibular Asymmetry in Class II Subdivision cases from a Sample Pakistani Population. Ann Jinnah Sindh Med Uni 2019; 5(2):71-76
16. Lin H, Zhu P, Lin Y, Wan S, Shu X, Xu Y and Zheng Y. Mandibular asymmetry: a three-dimensional quantification of bilateral condyles. Head Face Med. 2013;9(1):1-7. (DOI: 10.1186/1746-160X-9-42)
17. Kasimoglu Y, Tuna EB, Rahimi B, Marsan G, Gencay K. Condylar asymmetry in different occlusion types. CRANIO®, 33:1, 10-14, (DOI 10.1179/0886963414Z.00000000039)

18. Sofyanti, Ervina & Nainggolan, Lidya Irani & Ramakrishnan, Thivashini. (2018). Difference of Vertical Mandibular Symmetry Based on Mandibular Growth Pattern in Orthodontic Patients. 10.2991/idcsu-17.2018.25. (DOI:10.2991/idcsu-17.2018.25)

19. Saglam AM, Sanli G. Condylar asymmetry measurements in temporomandibular disorders. J Contemp Dent Pract. 2005;5:59- 65. (DOI: 10.5005/jcdp-5-3-59)

20. Millers VJ, Smidt A. Condylar asymmetry and age in patients with Angle class II division 2 malocclusion. J Oral Rehabil. 1996; 23:712-15.

21. Thiesen G, Freitas MPM, Gribel BF, Kim KB.Comparison of maxillomandibular asymmetries in adult patients presenting different sagittal jaw relationships. Dental Press J Orthod. 2019;24(4):54-62. (doi: 10.1590/2177-6709.24.4.054-062.oar)

22. Kurt G, Uysal T, Sisman Y, Ramoglu SI. Mandibular Asymmetry in Class II Subdivision Malocclusion. Angle Orthod. 2008;78:32-7. (DOI: 10.2319/021507-73.1)

23. Al Taki A, Ahmed MH, Ghani HA, Al Kaddah F. Impact of different malocclusion types on the vertical mandibular asymmetry in young adult sample. Eur J Dent 2015; 9: 373-77. (DOI: 10.4103/1305-7456.163233)

24. Syeda AA, Roohi U. Evaluation of condylar asymmetry in class II division 1 malocclusion patients a comparative radiographic study. Indian Journal of Orthodontics and Dentofacial Research. 2015; 1(1):11-15.

25. Millers VJ, Bodner L. Condylar asymmetry measurements in patients with Angle class III malocclusion. J Oral Rehabil. 1997; 24:247- 49. (DOI: 10.1111/j.1365-2842.1997.tb00322.x)

Original Article **Open Access**

Lipid Profile Abnormalities in ß-Thalassemia Patients with Multiple Blood Transfusions

Syeda Sabahat Haidar, Mehvish Sana, Rukhsana Tumrani, Farwa Shafqat

ABSTRACT

Objective: To determine lipid profile abnormalities in ß -thalassemia patients with multiple blood transfusions in tertiary care hospital.

Study design and setting: This cross-sectional study was conducted in Chemical Pathology section, Pathology department Sheikh Zayad Medical College and Hospital Rahim Yar Khan from 1st July 2022 to 31st October 2022.

Methodology: 110 patients aged 1 to 18 years from both genders enrolled in Thalassemia center of Sheikh Zayed Hospital with multiple blood transfusions were included in study using convenient sampling technique. Patients with cardiac disease, diabetes mellitus and family history of lipid disorders were excluded. Blood samples collected from thalassemia patients were subjected to estimation of serum total cholesterol, serum triglycerides, HDL-C, and LDL-C. Data was recorded on predesigned performa. Post stratification t test was applied and p value <0.05 was considered significant.

Results: Mean age of the patients was 7.77±3.846 years. Mean serum cholesterol, serum triglyceride, HDL-C and LDL-C were 89.15±20.33mg/dl, 211.00±77.78mg/dl, 21.01±6.554mg/dl and 29.79±17.02 respectively. Mean triglyceride and LDL-C level was higher in patients with weekly transfusion than patients undergoing monthly transfusion with statistically significant difference of triglycerides and LDL-C between two groups with p=0.002 and 0.023 respectively.

Conclusion: We found that frequent blood transfusion causes lipid profile abnormalities in thalassemia patients. Lipid profile abnormalities should be screened frequently in ß-thalassamia patients with multiple blood transfusions.

Keywords: Atherosclerosis, Blood transfusion, Iron overload, Lipid profile, ß-Thalassemia.

How to cite this Article:
Haider SS, Sana M, Tumrani R, Shafqat F. Lipid Profile Abnormalities in ß-Thalassemia Patients with Multiple Blood Transfusions. J Bahria Uni Med Dental Coll. 2023;13(4):296-9 DOI: https://doi.org/10.51985/JBUMDC2022160

INTRODUCTION:

Thalassemia is an inherited autosomal recessive microcytic hypochromic anemia resulting from hereditary defect in hemoglobin synthesis affecting production of alpha or ß globin chains. The results are disproportionate production of alpha or ß globin chains.[1] Individuals with thalassemia either have an absolute defect in synthesis of ß globin chains and therefore absence of ß chains called ß-thalassemia major (Cooley's anemia) or partially decreased production of ß chain called ß-thalassemia minor while thalassemia intermedia a group of patients with ß thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of ß thalassemia trait and the severe manifestations of ß thalassemia major. The diagnosis is a clinical one made on the basis of the patient maintaining a satisfactory Hemoglobin level of at least 6-7 g/dl without the need for regular blood transfusions.[2] In ß-thalassemia major there is severe impairment in ß-globin chain production and this synthetic imbalance leads to ineffective erythropoiesis and hemolytic anemia making regular blood transfusion only means of survival for these individuals.[3] Thalassemia gene is carried by 3% population of the world. A higher thalassemia prevalence has been reported in Central Asia, Middle East, and Mediterranean countries.[4] Pakistan is estimated to have a carrier rate of 5-7%, with overall 9.8 million carriers in the population.[5] High frequency of this hemoglobin disorder compared with other monogenic diseases is mediated by high frequency of consanguineous marriages in many countries[3] including Pakistan. ß-thalassemia patients have significantly low levels of cholesterol associated with their disease and remains unaffected by age, gender, hemoglobin, or ferritin levels.[6]

Syeda Sabahat Haidar
Associate professor, Department of Pathology
Sheikh Zayed Medical College/Hospital Rahim Yar Khan
Email: sabahattariq@gmail.com

Mehvish Sana *(Corresponding Author)*
Demonstrator, Department of Pathology
Sheikh Zayed Medical College/Hospital Rahim Yar Khan
Email: Sanamehvish1983@hotmail.com

Rukhsana Tumrani
Resident, Department of Pathology
Sheikh Zayed Medical College/Hospital Rahim Yar Khan
Email: r.tumrani333@gmail.com

Farwa Shafqat
Student of Final year MLT
Sheikh Zayed Medical College/Hospital Rahim Yar Khan

Received: 29-12-2023
Accepted: 20-09-2023

In transfusion dependent ß-thalassemia patients liver is the primary organ to deposit iron causing damage to both hepatocyte and reticulo-endothelial cells which may lead to liver fibrosis. Liver damage is evinced by elevated liver enzymes and triglycerides while serum total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) are decreased.[7,8] The pathophysiology of hypocholesterolemia in thalassemia is uncertain, although various mechanisms have been suggested including increased cholesterol requirement associated with erythroid hyperplasia, plasma dilution attributable to anemia and high cholesterol consumption by the reticuloendothelial system.[7] Thalassemia is a condition of secondary iron overload. Frequent blood transfusions and increased iron absorption from gut both contribute to iron overload.[9] Iron overload can lead to many complications in thalassemia patients including lipid profile derangement.[10] In iron overload patients free radical production is increased through Fenton reaction. These free radicals accumulate in liver, heart, and other organs causing immense tissue damage. A high incidence of endothelial dysfunction, atherogenesis and thromboembolic event has been reported in thalassemia patients most probably due to abnormality in lipid profile related to transfusion iron overload in liver. There is also increased risk of cardiovascular complications and pancreatitis due to atherogenesis and high triglyceride level respectively.[10]

This study aims to observe the lipid profile abnormalities in ß-thalassemia patients so as to guide the pediatricians and staff of thalassemia center for routine screening of lipid abnormalities in these patients in order to prevent the cardiovascular complications due to lipid profile abnormalities and mortality due to these complications.

METHODOLOGY:

This cross-sectional study was conducted in Chemical Pathology section, Pathology department of Sheikh Zayed Medical College and Hospital Rahim Yar Khan for 4 months from 1st July 2022 to 31st October2022. 110 patients aged 1 to 18 years from both genders enrolled in Thalassemia center of Sheikh Zayed Hospital with more than 1 year of regular blood transfusions were included in study using convenient sampling technique after obtaining ethical approval from institutional review board (474/IRB/SZMC/SZH dated 11/6/2022). Informed consent was taken from patients and their parents. Patients with cardiac disease, diabetes mellitus. family history of lipid disorders and not willing to be included in study were excluded. Blood samples were collected in gel tubes which were centrifuged after 30 minutes of collection to obtain clear serum. Serum of each patient was subjected to estimation of serum total cholesterol, serum triglycerides and HDL-C. LDL-C concentrations were determined by Friedewald's formula. All tests were performed on Atellica CH 930 fully automated chemistry analyzer based on spectrophotometry. Age, gender, weekly or monthly transfusion status and all the test results were recorded on predesigned performa. Data was entered and analyzed using SPSS 20. Qualitative data was presented as frequency and percentage while quantitative data was given as mean and SD. Post stratification t-test was applied and p value <0.05 was taken as significant.

RESULTS:

One Hundred and Ten ß-thalassemia patients with multiple blood transfusions were included in study among which 60(54.5%) were males and 50(45.5%) were females. 77(70%) patients were in 1-9 years age group while 33(30%) were

Table 1: Lipid profile abnormalities in ß-thalassemia patients with respect to age

Lipid profile	1-9 years	10-18 years	p-value
Total cholesterol mg/dl	90±20	85±20	0.163
Triglyceride mg/dl	222±76	183±75	0.016
HDL-C mg/dl	21±7.6	20±2.5	0.458
LDL-C mg/dl	29±16	30±18	0.850

Figure 1: Transfusion frequency of patients

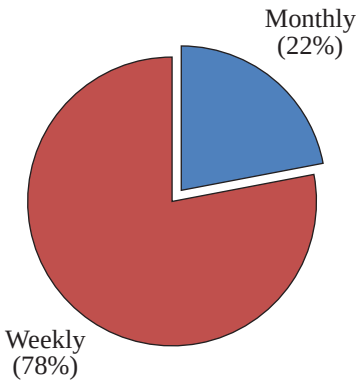


Table 2: Transfusion frequency and lipid profile abnormalities in ß-thalassemia patients

Lipid profile	Weekly Transfusion	Monthly Transfusion	p-value
T.cholesterol mg/dl	88±20	90±18	0.765
Triglyceride mg/dl	222±81	169±44	0.002
HDL-c mg/dl	20±7.0	21±4.6	0.712
LDL-c mg/dl	27±16	36±17	0.023

Table 3: Lipid profile derangement in ß-Thalassemia major patients

Lipid profile	(mean±SD)
T. cholesterol (mg/dl)	89.15±20.33
Triglyceride (mg/dl)	211.00±77.78
HDL-C (mg/dl)	21.01±6.554
LDL-C (mg/dl)	29.79±17.02

in 10-18 years age group. Mean age of the patients was 7.77±3.846 years. Mean triglyceride level in 1–9-year age group was 222±76 mg/dl, while in 10–18-year age group was 183 ±75 mg/dl with statistically significant difference between two groups (p=0.016) as shown in table 1 while difference of serum total cholesterol, HDL-C and LDL-C was statistically insignificant in two age groups. 86(78%) patients were on weekly transfusion while 24(22%) were on monthly transfusion as shown in figure 1. Mean triglyceride level in patients undergoing weekly transfusion was 222±81 mg/dl and in patients with monthly transfusion was 169±44 mg/dl with statistically significant difference of triglycerides between two groups (p=0.002). Mean LDL-C level in patients with weekly transfusion was 27±16 mg/dl and in patients with monthly transfusion was 36±17 mg/dl with statistically significant difference of LDL-C between two groups (p=0.023). Total cholesterol and HDL-C were slightly lower in patients undergoing weekly transfusion than monthly transfusion patients but difference was not statistically significant as shown in table 2. Overall High serum triglyceride and low serum cholesterol, HDL-C and LDL-C levels were observed in ß-thalassemia patients as compared to reference values of these analytes as shown in table 3.

DISCUSSION:

In our study ß-thalassemia patients had high triglyceride level while total cholesterol, HDL-C, LDL-C were low as compared to reference values of these analytes. Serum triglyceride was higher in 1-9 years age group as compared to 10-18 years age group and difference of serum triglyceride between these two age groups was statistically significant. The mean value of Triglyceride (mg/dl) of thalassemia patients in our study was (mean±SD) 211.00±77.78 mg/dl. Higher triglyceride level was observed in patients with weekly transfusion than monthly transfusion patients and difference was statistically significant (p=0.002). The mean serum total cholesterol, HDL-C and LDL-C of thalassemia patients in our study was 89.15±20.33 mg/dl, HDL-C 21.01±6.554 mg/dl and LDL-C 29.79±17.02 mg/dl respectively. A study conducted in Basrah, Iraq showed significantly lower serum total cholesterol, HDL-cholesterol and LDL-cholesterol and significantly higher serum triglyceride in ß-thalassemia major patients as compared to controls ($p<0.05$).[11] Saleh et al reported hypocholesterolemia, hypertriglyceridemia with low levels of HDL-C and LDL-C in ß-thalassemia major patients.[12] A study conducted in northwestern India reported lower total cholesterol and HDL-C in thalassemia patients as compared to controls ($p<0.001$ for both) while triglyceride was higher in thalassemia patients as compared to controls ($p<0.001$).[13] A higher total cholesterol/HDL ratio was also reported in this study.[13] Dyslipidemia was characterized by high triglyceride, low HDL and high cholesterol/HDL ratio in transfusion dependant patients in Eastern India.[14] Dey et al and Mashaali et al reported HDL-C value of 36.58±12.22 mg/dl which was on lower side of their reportable range.[15,16] Dyslipidemia in ß-thalassemia major patients irrespective of age and gender was reported in a Southern Pakistan study.[17] A study conducted in Swat, Pakistan showed high level of serum triglyceride and low level of serum cholesterol and HDL-C in thalassemia patients.[18] Findings of our study are in line with above given reports as hypertriglyceridemia, hypcholesterolemia, lower HDL-C and LDL-C were observed in our study. Inati et al conducted a study in Lebanon and reported altered lipid profile in ß-Thalassemia major patients. In this study lower levels of serum total cholesterol and LDL-C were observed in thalassemia major patients than healthy controls, while no significant difference was observed in serum triglycerides levels of thalassemia patients and controls.[19] A double blind randomized controlled trial of curcumin showed significant decrease in triglyceride as compared to placebo group ($p=0.038$).[20] Main mechanism proposed for this dyslipidemia was severe iron overload, accelerated erythropoiesis, oxidative stress and increased cholesterol utilization.[21] Liver failure due to iron overload, cytokine release, macrophage system activation and hormonal disturbance may also contribute to lipid abnormality.[22] HDL and LDL cholesterol are key components of the lipid profile. Several epidemiological studies have confirmed low HDL-C as a predictive biomarker for atherosclerotic cardiovascular diseases including ischemic heart disease and myocardial infarction.[23] Early identification of thalassemia patients with a altered lipid profile is essential to prevent thrombotic and atherogenic complications. Patients with altered lipid profile particularly hypertriglyceridemia and low HDL-C should be advised dietary and lifestyle modifications and if it is not controlled by these then lipid-lowering agents may be started. Increasing awareness of thalassemia in general population by awareness campaigns, earlier identification, increased blood donation and blood availability for transfusion, modern therapy in iron chelation and proper follow up makes this disease easier to handle.

CONCLUSION:

It is concluded that frequent blood transfusion causes lipid profile abnormalities in thalassemia patients. Lipid profile abnormalities should be screened frequently in ß-thalassamia patients with multiple blood transfusions as these patients are at risk of atherosclerosis and cardiovascular disease due to altered lipid profile particularly high triglyceride and low HDL-C. Therefore diagnosis, awareness and treatment of lipid profile abnormalities is helpful in these patients for prevention of cardiovascular events.

Authors Contribution:
Syeda Sabahat Haidar: Conception and design
Mehvish Sana: Manuscript writing, data analysis, interpretation
Rukhsana Tumrani: Data analysis and interpretation
Farwa Shafqat: Data collection

REFERENCES:

1. Ragab SM, Safan MA, Sherif AS. Lipid profiles in ß thalassemic children. Menoufia Med J 2014; 27(1):66 DOI: https://doi.org/10.4103/1110-2098.132749
2. Suman R, Sanadhya A, Meena P, Singh J, Jain R, Meena S. Lipid profile in children of ß-thalassemia mayor and their correlation with serum ferritin. Int J Contemp Pediatr 2017 Mar; 4(2):543-7
3. Origa R. ß-Thalassemia. Genet Med 2017 ;19(6):609-19 DOI: https://doi.org/10.1038/gim.2016.173
4. Ali S, Mumtaz S, Shakir HA, Khan M, Tahir HM, Mumtaz S, et al. Current status of beta-thalassemia and its treatment strategies. Mol Genet Genomic Med 2021;9(12):e1788 DOI: https://doi.org/10.1002/mgg3.1788
5. Akhtar S, Nasir JA, Hinde A. The prevalence of hepatitis C virus infection in ß-thalassemia patients in Pakistan: a systematic review and meta-analysis. BMC Public Health 2020; 20(1):1-9 DOI: https://doi.org/10.1186/s12889-020-8414-5
6. Wibowo TS, Ashariati A, Bintoro S, Soeslistijo SA. Serum Ferritin Levels and Lipid Profile in Patients with Transfusion-Dependent Beta and Beta/HbE Thalassemia. Int J Pharm Res 2020; 12(4)
7. Balcý YI, Ünak Þ, Gümrük F. Serum Lipids in Turkish Patients with ß-Thalassemia Major and ß-Thalassemia Minor. Turk J Hematol 2016; 33:71-83
8. Maira D, Cassinerio E, Marcon A, Mancarella M, Fraquelli M, Pedrotti P, et al. Progression of liver fibrosis can be controlled by adequate chelation in transfusion-dependent thalassemia (TDT). Ann Hematol 2017;96:1931-6 DOI: https://doi.org/10.1007/s00277-017-3120-9
9. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology Am Soc Hematol Educ Program 2017; 2017(1):265-71 DOI: https://doi.org/10.1182/asheducation-2017.1.265
10. Nandi S, Samanta S, Mondal T, Halder S. Study of lipid profile in ß thalassemia major pediatric patients with multiple blood transfusion and its correlation with serum ferritin level in tertiary care hospital in Kolkata. Int J Community Med Public Health 2021; 8(4):1778 DOI: https://dx.doi.org/10.18203/ 2394-6040.ijcmph20211233
11. Jabbar HK, Hassan MK, Al-Naama LM. Lipids profile in children and adolescents with ß-thalassemia major. Hematol Transfus Cell Ther 2022 DOI: https://doi.org/10. 1016/j.htct.2022.09.1277
12. Saleh KK, Abdullah SR, Mekha RE. Estimation of Serum Homeostasis Model Assessment-Insulin Resistance and Lipid Profile in Beta-thalassemia Major Patients and their Correlation with Iron Overload in Koya City. Polytechnic J 2019; 9(2):125-32 DOI: https://doi.org/10.25156/ptj.v9n2y2019.pp125-132
13. Daswani P, Garg K. Lipid profile in?-thalassemia major children and its correlation with various parameters. Indian J Child Health 2021; 8(1):26-31 DOI: https://doi.org/10.32677/IJCH.2021.v08.i01.005
14. Kumar T, Basu S, Kundu R, Majumdar I, Mukherjee D. Lipid profile in children with thalassemia: A prospective observational study from eastern India. Indian pediatrics 2020 Nov; 57:1072-3 DOI: https://doi.org/10.1007/s13312-020-2040-2
15. Dey A, Sandip C, Arya S. dkk. Correlation of serum lipid profile with serum iron, TIBC & ferritin levels in beta thalassemia major patients. Eur J Biol and Med Sci Res 2016; 4:17-26
16. Mashaali JK, Obed FA, Thair NT. Lipid Profile in Iraqi Children with ß-thalassemia Major. Iraqi J Hematol 2014; 3(2):108
17. Ashar S, Sultan S, Irfan SM, Sheeraz A. Serum fasting lipid profile in children and adolescents with ß-thalassaemia major in southern Pakistan. Malay J Pathol 2015; 37(3)
18. Asif M, Rasheed A. Dyslipidemia in beta thalassemia major patients. J Saidu Med Col 2015; 5(2):695-7
19. Inati A, Noureldine MA, Mansour A, Abbas HA. Endocrine and bone complications in ß-thalassemia intermedia: current understanding and treatment. BioMed Res Int 2015; 2015 DOI: https://doi.org/10.1155/2015/813098
20. Tamaddoni A, Nasseri E, Mohammadi E, Qujeq D, Zayeri F, Zand H, et al. A double-blind randomized controlled trial of curcumin for improvement in glycemic status, lipid profile and systemic inflammation in ß-thalassemia major. J Herb Med 2020;21:100324 DOI: https://doi.org/10.1016/j.hermed.2019.100324
21. Setoodeh S, Khorsand M, Takhshid MA. The effects of iron overload, insulin resistance and oxidative stress on metabolic disorders in patients with ß-thalassemia major. J Diabetes Metab Disord 2020; 19:767-74
22. Boudrahem-Addour N, Izem-Meziane M, Bouguerra K, Nadjem N, Zidani N, Belhani M, et al. Oxidative status and plasma lipid profile in ß-thalassemia patients. Hemoglobin 2015;39(1):36-41 DOI: https://doi.org/10.3109 /03630269.2014.979997
23. Casula M, Colpani O, Xie S, Catapano AL, Baragetti A. HDL in atherosclerotic cardiovascular disease: in search of a role. Cells 2021; 10(8):1869

Original Article **Open Access**

Prognosis of RUNX1-RUNX1T1 Rearrangement in Newly Diagnosed Acute Myeloid Leukemia Patients

Halima Babar, Hamid Saeed Malik, Muhammad Umar, Zahra Tasleem

ABSTRACT

Objective: To compare the clinical-hematological (including laboratory and morphological) parameters of newly diagnosed AML patients with RUNX1-RUNX1T1 rearrangement before and after induction therapy.

Study Design and Setting: This is a cross-sectional study, Department of Hematology, Armed Forces Institute of Pathology (AFIP), Rawalpindi from December 2021 to December 2022.

Methodology: 64 newly diagnosed patients with de novo t (8;21) AML were included. The RUNX1-RUNX1T1 fusion gene was detected using real-time reverse transcriptase polymerase chain reaction (RT-PCR); while t(8;21) was identified through chromosomal/cytogenetic analysis. All the clinical parameters, laboratory variables, blast percentages, and morphological parameters of newly diagnosed AML RUNX1-RUNX1T1 patients were compared before and after therapy. AML induction regimen included the following drugs: cytarabine along daunorubicin. Assessment of these patients was carried out four weeks after induction therapy.

Results: The patients' mean age was 60 (ranging from 14 to 85 years), with 46 males and 18 females. Statistical significance was observed in TLC (p-value < 0.001), Hb (p= 0.001), and platelet count(p=0.001) levels. After treatment, the blast size in peripheral blood was reduced to zero and both Auer rods and abnormal granules were absent in bone marrow blasts of patients. The average percentage of eosinophilia decreased from 8.52±1.76 before treatment to 2.42±1.79 after treatment.

Conclusions: Our study concluded that the treatment approach(cytarabine along with daunorubicin or idarubicin) for patients with RUNX1-RUNX1T1 AML resulted in improved blood counts, reduced blast cells, Auer rods, and abnormal granules; with a higher rate of complete remission and a lower incidence of relapse.

Keywords: Acute myeloid leukemia, AML with t (8;21), Complete Remission, Prognosis, RUNX1-RUNX1T1

How to cite this Article:
Babar H, Malik HS, Umar M, Tasleem Z, Tahir N. Prognosis of RUNX1-RUNX1T1 Rearrangement in Newly Diagnosed Acute Myeloid Leukemia Patients. J Bahria Uni Med Dental Coll. 2023;13(4):300-4 DOI: https://doi.org/10.51985 /JBUMDC2023239

INTRODUCTION:

Acute myeloid leukemia (AML) is characterized by malignant clonal proliferation of progenitor cells in conjunction with differentiation arrest. The annual occurrence of AML, adjusted for age, in the United States (US), is 4.3 cases per 100,000 individuals. The frequency of occurrence rises as individuals get older, with a typical age of diagnosis being 68 years.[1] Unusual development of myeloid cells leads to an elevated presence of immature malignant cells and a reduced number of fully developed red blood cells, platelets, and white blood cells. AML's clinical appearance upon diagnosis might range from an accidental finding on a routine blood test to a life-threatening condition requiring immediate attention. AML is distinguished by the following characteristics, in addition to general symptoms such as exhaustion and loss of appetite: Anemia causes exhaustion and weakness of breath when exerted; neutropenia causes recurring infections; and thrombocytopaenia causes a higher susceptibility to bruising and bleeding. Untreated AML often leads to bone marrow failure, resulting in life-threatening symptoms that manifest rapidly over a span of weeks or months.[2] Acute leukemia is diagnosed when the bone marrow or peripheral blood contains 20% or greater numbers of blasts.[3] AML classification shifted from morphology to genetic-based, WHO includes AML with recurrent genetic

Halima Babar
Registrar, Department of Pathology-Hematology
Armed Forces Institute of Pathology Rawalpindi-Pakistan
Email: hb.2293@ymail.com

Hamid Saeed Malik
Consultant, Department of Pathology-Hematology
Armed Forces Institute of Pathology Rawalpindi-Pakistan
Email: hamidsaeed819@gmail.com

Muhammad Umar
Registrar, Department of Pathology-Hematology
Armed Forces Institute of Pathology Rawalpindi-Pakistan
Email: muhammadumar14397@gmail.com

Zahra Tasleem
Registrar, Department of Pathology-Hematology
Armed Forces Institute of Pathology Rawalpindi-Pakistan
Email: khanzt4@gmail.com

Nazish Tahir
Registrar, Department of Pathology-Hematology
PNS SHIFA Karachi
Email: hosh.009@hotmail.com

Received: 01-08-2023
Accepted: 10-09-2023

abnormalities indicating specific changes.[4] The most significant indicators of prognosis in acute myelogenous leukemia (AML) are cytogenetic and morphological characteristics which have been used in diagnosis and therapy, as well as in understanding their pathogenesis.[5]

Acute myeloid leukemia (AML) with t (8;21) (q22; q22.1), accounts for approximately 4% to 8% of all AML cases. According to the FAB classification, this particular subtype is linked to the M2 subtype. It tends to occur in younger individuals, exhibits a distinct immunophenotype, frequently expresses CD19, and shows various additional cytogenetic abnormalities such as loss of a sex chromosome, deletion of the 9th long arm of chromosome 9, trisomy 8, all of which collectively contribute to a favorable prognosis.[6] The t (8;21) (q22; q22.1) translocation is an oncogenic change that results in the formation of a new hybrid gene, RUNX1-RUNX1T1, formed on the altered chromosome 8. This translocation produces a merged gene combining the chromosome 21 RUNX1 gene with the chromosome 8 RUNX1T1 gene (also called ETO) gene.[7] This subtype of AML is found to have a higher expected rate of complete remission (CR) and is associated with a favorable long-term outcome and lower incidence of relapse. The European Leukemia Net (ELN) considers the translocation t(8;21) and the resulting RUNX1-RUNX1T1 gene fusion as a favorable subset in AML risk stratification in 2017.[8] Both RUNX1 and RUNX1T1 play a crucial role in a transcriptional complex responsible for regulating significant target genes implicated in hematopoiesis.[9] The AML1-ETO (RUNX1-RUNX1T1) fusion product alters the core binding factor transcription complex, affecting proliferation, cell differentiation, apoptosis, and self-renewal which results in the induction of leukemogenesis.[10]

The purpose of the study is to compare the clinical-hematological (including laboratory and morphological) parameters of diagnosed RUNX1-RUNX1T1 AML patients before and after therapy. Complete remission (CR) of each AML patient post-induction therapy was determined and taken into account. Thus, this study determined the prognosis of RUNX1-RUNX1T1 in the Pakistani population.

METHODOLOGY

This cross-sectional study was performed at the Armed Forces Institute of Pathology (AFIP), Rawalpindi from December 2021 to December 2022 after taking approval from the Institutional Review Board (IRB), vide reference number OA-239-2023 After a thorough literature search, we calculated a sample size of 64 via the WHO calculator, keeping the margin of error at 5%, a confidence level at 95%, and AML prevalence at 4.3%.[1] Sampling was done using a non-probability consecutive sampling technique.

Patients of all ages and both genders who were newly diagnosed with AML with RUNX1-RUNX1T1 gene rearrangement were included in this study. Patients with acute leukemias other than AML, patients of AML with other recurrent genetic abnormalities, and AML patients already undergoing therapy were excluded.

Written consent was obtained before enrolling all patients and their confidentiality was ensured at all levels. Approval of the institutional ethical committee was also procured before starting the project. In this study, 64 newly diagnosed patients with de novo t(8;21) AML were included. The RUNX1-RUNX1T1 fusion gene was detected using real-time reverse transcriptase polymerase chain reaction (RT-PCR), while t(8;21) was identified through chromosomal/cytogenetic analysis. All patients underwent evaluation at the time of diagnosis and following induction therapy i.e. after four weeks. Clinical parameters such as age, gender, and organomegaly (hepatomegaly, splenomegaly) were observed. EDTA anti-coagulated blood sample from each patient was analyzed using the Sysmex XN 3000 automated hematology analyzer to record laboratory variables, including total leucocyte count (TLC), hemoglobin (Hb), and platelet count. The normal ranges for laboratory variables included: TLC (4-10)×10^9/L, Hb (13-17)g/dL, and platelets (150-450)×10^9/L.

Additionally, a bone marrow aspirate sample was obtained and subjected to cytochemical staining to determine blast percentages and morphological parameters, such as blast size, Auer rods, abnormal granules, and eosinophilia. Cytogenetics and molecular evaluation were done after obtaining blood/bone marrow samples from each patient in our study, before starting induction treatment. Cytogenetics used the FISH (fluorescence in-situ hybridization) technique.

All the clinical parameters, laboratory variables (including blast percentages), and morphological parameters of newly diagnosed AML RUNX1-RUNX1T1 patients were compared before and after therapy. AML induction regimen includes the following drugs: cytarabine along with daunorubicin or idarubicin. CR (Complete Remission) criteria according to WHO comprises of Neutrophil count: $=1x10^9$/L, Platelet count: $=100x10^9$/L, <5% myeloblasts without Auer rods in peripheral blood, transfusion independence and no splenomegaly (or no extramedullary disease).

Collected data was processed through SPSS 24, using standard protocol analysis. Baseline variables were analyzed descriptively using frequencies and percentages for qualitative variables and mean with standard deviation for continuous variables like pre-treatment and after-treatment. Statistically significant differences before and after intervention were assessed using Paired sample t-tests for continuous variables. Post-stratification chi-square test was applied for qualitative variables taking p-value = 0.05 as significant to check for a potential association between variables and response.

RESULTS:

In this study, a total of 64 patients diagnosed with de novo t(8;21)/RUNX1-RUNX1T1 AML were carefully selected

for enrollment. The mean age of the patients was found to be 60.0 years, with a range of 14 to 85 years. Among these patients, 46 (71.9%) were male, while 18 (28.1%) were female, as shown in Figure 1. Prior to treatment, their mean total leukocyte count (TLC) was 12.53±6.51 (x109/L), hemoglobin (Hb) level was 9.08±1.82 g/dL, and platelet count was 86.25±12.46 (x109/L). After treatment, the study observed a significant improvement in the TLC count, as well as a rise in both Hb and platelet counts. The mean TLC count after treatment was 8.06±2.04 (x109/L), Hb level was 11.03±1.48g/dL, and platelet count was 154.98±19.93 (x109/L). These improvements were statistically significant, with a p-value of less than 0.001 for TLC, and a p-value of 0.001 for both Hb and platelet count, as shown in Table I. This data provides valuable insights into the effectiveness of the treatment for de novo t(8;21)/RUNX1-RUNX1T1 AML, which can help improve patient care and outcomes.

Before treatment, larger-sized blasts (mean= 24.03±3.94%) were observed both in the peripheral blood and bone marrow. While after treatment, the blast count in peripheral blood and bone marrow was zero and <5%, respectively; a reduction in blast size was (mean: 3.35±1.05%) was also observed. Before treatment, Auer rods in myeloblasts were present in 98.4% of patients (n=63) and abnormal granules (also in myeloblasts) in 96.9% of patients (n=62). Following the induction therapy, it was observed that less than 5% of the circulating bone marrow myeloblasts contained Auer rods, indicating positive progress. Additionally, the percentage of abnormal granules in these blasts was significantly reduced, indicating an improvement in the condition. Prior to the induction therapy, the average percentage of eosinophilia was 8.52±1.76%. However, after the treatment, the percentage of eosinophilia reduced significantly to 2.42±1.79%, reflecting the effectiveness of the therapy. Table II presents a comparative analysis of the morphological characteristics of patients with AML with RUNX1-RUNX1T1 gene rearrangement before and after treatment. The analysis revealed a statistically significant difference between the morphological features of the patients before and after treatment, with a p-value of 0.001.

Figure 1: Distribution of patients according to gender

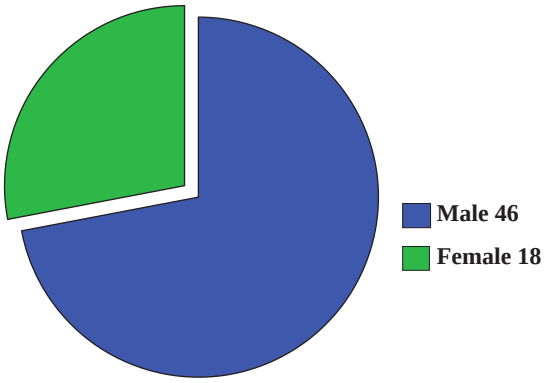


Table 1: Comparison of clinical and laboratory findings in AML with RUNX1-RUNX1T1 patients before and after treatment (n=64)

Parameters	Before	After	p-value
TLC ($x10^9$/L)	12.53±6.51	8.06±2.04	< 0.001
Hemoglobin (g/dL)	9.08±1.82	11.03±1.48	0.001
Platelet ($x10^9$/L)	86.25±12.46	154.98±19.93	0.001
Blast count (%)	50±30	3±2	0.001

Table 2: shows a statistically significant difference in morphological characteristics of newly diagnosed AML with RUNX1-RUNX1T1 patients before and after treatment (p-value of 0.001)

Parameters	Before Treatment	Before Treatment	p-value
Large blasts (%)	24.03±3.94	24.03±3.94	0.001
Auer rods (BM blasts)			
Present	63 (98.4%)	63 (98.4%)	0.001
Absent	1 (1.6%)	1 (1.6%)	
Abnormal granules			
Present	62 (96.9%)	62 (96.9%)	0.001
Absent	2 (3.1%)	2 (3.1%)	
Eosinophilia (%)	8.52±1.76	8.52±1.76	0.001

DISCUSSION:

AML is diagnosed by the presence of =20% blast cells of myeloid lineage in the peripheral blood and/or bone marrow.[11] Certain gene mutations are vital for managing the risk and clinical categorization of individuals with AML.[12] The chromosomal rearrangement t(8;21) is a well-acknowledged genetic abnormality in AML, that is usually observed in 5-12% of individuals with acute myeloid leukemia (AML) and is most commonly associated with AML with maturation (FAB type AML-M2).[13] According to recent studies, patients diagnosed with acute myeloid leukemia (AML) who have the RUNX1-RUNX1T1 rearrangement may benefit from intensive consolidation therapy as part of their treatment regimen. This type of therapy involves high doses of cytarabine, a medication that helps to destroy cancer cells. The studies suggest that patients with this particular genetic mutation who receive intensive consolidation therapy demonstrate improved rates of complete remission and long-term disease-free survival (DFS). These findings could have significant implications for the treatment of AML patients with the RUNX1-RUNX1T1 rearrangement, potentially leading to more effective and personalized treatment plans.[14-15] In classical t(8;21) AML patients, the utilization of anthracycline and cytarabine induction chemotherapy leads to remission rates reaching approximately 90%.[16-17]

Our study examined treatment response in 64 de novo t(8;21)/RUNX1-RUNX1T1 AML patients. Notably, male patients (46) outnumbered females (18) in the study. Pre-treatment blood parameters indicated compromised health. The mean Total Leukocyte Count (TLC) was 12.53±6.51 ($x10^9$/L), reflecting elevated white blood cell levels in the

majority of the patients taken in our research study. Hemoglobin (Hb) levels were below normal (mean: 9.08±1.82 g/dL) and platelet counts were also reduced (mean: 86.25±12.46 $x10^9$/L). After receiving treatment (cytarabine along with daunorubicin or idarubicin), positive changes were noted in the blood parameters/variables of the patients. There was a notable reduction in the TLC, with the average post-treatment TLC decreasing to 8.06±2.04 ($x10^9$/L). This decrease in TLC following therapy signifies a favorable treatment response and could potentially help relieve the burden of leukemia in the patients. Hb levels of patients rose significantly after treatment (mean: 11.03±1.48 g/dL). Platelet counts also increased notably (average: 154.98±19.93 $x10^9$/L). Morphological analysis showed promising results. Initially, the majority of the patients (98.4%) had Auer rods and abnormal granules (96.9%) found in the peripheral blood and bone marrow myeloblasts.

A 62-year-old woman was discussed in a case study by Lindsey *et al*,[17] When she was admitted to the hospital, her white blood cell count was 5 x 10^3/ìL with 17% blasts, her hemoglobin was 9.1 g/dL, and her platelet count was 22 × 10^3/ìL. The results of her bone marrow biopsy showed a significant population of blasts with round to irregular, intermediate-sized nuclei, prominent nucleoli, and scant to moderate cytoplasm; 59% blasts according to manual count. The translocation t(8;21) was detected in this patient using both conventional cytogenetics as well as FISH technique. The patient received conventional idarubicin and cytarabine treatment. The only complication was neutropenic fever, which had no identifiable infectious source. The treatment was successful as the patient achieved complete cytogenetic response (CCyR), maintaining this response for 18 months.

Another case of a 63-year-old female was also described by Lindsey *et al*,[17] The patient's WBC count was measured to be 6.1 × 10^3/ìL, with 67% of these cells being myeloblasts on peripheral blood examination. Additionally, her Hb level was 9.1 g/dL, and her platelet count was 4 × 10^3/ìL. A bone marrow biopsy revealed that the number of blasts had increased to 75% according to the estimated count. The patient was diagnosed as having AML with RUNX1-RUNX1T1 gene mutation (fusion detected on PCR). The patient received conventional idarubicin and cytarabine induction treatment, which helped her achieve a complete cytogenetic remission. Patients with the chromosomal rearrangement t(8;21), generally have a lower chance of experiencing a relapse.

Similarly, in their study, Kim *et al*,[18] found that Auer rods were present in 67% (14/21) of patients with AML-M2 in whom t(8;21) was found. The study also showed that blast cells with Auer rods and a high number of abnormal granules were more commonly observed in patients who tested positive for RUNX1-RUNX1T1 mutation. After treatment, Auer rods in <5% of bone marrow myeloblasts were nil and abnormal granules were scanty, indicating a positive cellular response. Our study showed that there was a significant decrease in eosinophilia following treatment. Following therapy, the percentage of myeloblasts in peripheral blood was reduced to zero and in bone marrow to <5%.

In a study conducted by the United Kingdom MRC, 5876 AML patients were analyzed, with 421 of them possessing the t(8;21) abnormality.[19] The results showed that this subset had a much better prognosis (p-value <0.001) and 61% long-term disease-free survival (DFS) rate, which is consistent with other studies.[20] In general, this study reveals that the therapeutic method is effective in treating de novo t(8;21) AML. The improvements in blood parameters, and morphological characteristics, including the reduction in blast count in both peripheral blood and bone marrow indicate a successful treatment outcome.

CONCLUSION:

In conclusion, this study offers valuable information on how patients with RUNX1-RUNX1T1 AML respond to therapy, with improvements in their blood counts. The treatment approach used resulted in significant rectification of TLC, Hb levels, and platelet count; as well as a reduction in blast cells, Auer rods, and abnormal granules. Moreover, the study indicates that the treatment approach has a higher rate of complete remission and a lower incidence of relapse. There are significant advances seen in terms of the treatment options available for AML patients since relapse is a common occurrence among these patients that can be challenging to manage.

Authors Contribution:
Halima Babar: Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
Hamid Saeed Malik: Data collection
Muhammad Umar: Data analysis
Zahra Tasleem: Literature search
Nazish Tahir: Data collection

REFERENCES:

1. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. Blood reviews. 2019;36:70-87. https://doi.org/10.1016/j.blre.2019.04.005
2. Khwaja A, Bjorkholm M, Gale RE, Levine RL, Jordan CT, Ehninger G, Bloomfield CD, Estey E, Burnett A, Cornelissen JJ, Scheinberg DA. Acute myeloid leukemia. Nat Rev Dis Primers. 2016;2(1):1-22. https://doi.org/10.1038 /nrdp.2016.10
3. Foucar K, Hsi ED, Wang SA, Rogers HJ, Hasserjian RP, Bagg A, George TI, Bassett Jr RL, Peterson LC, Morice WG, Arber DA. Concordance among hematopathologists in classifying blasts plus promonocytes: a bone marrow pathology group study. Int J Lab Hematol. 2020;42(4):418-22. https://doi.org/10.1111/ijlh.13212
4. Gudipati M, Butler M, Koka R, Baer MR, Ning Y. Fusion Gene-Based Classification of Variant Cytogenetic Rearrangements in Acute Myeloid Leukemia. Genes. 2023;14(2):396. https://doi.org/10.3390/genes14020396

5. Weinberg OK, Porwit A, Orazi A, Hasserjian RP, Foucar K, Duncavage EJ, Arber DA. The International Consensus Classification of acute myeloid leukemia. Virchows Archiv. 2023;482(1):27-37. https://doi.org/10.1007/s00428-022-03430-4
6. Appelbaum FR, Kopecky KJ, Tallman MS, Slovak ML, Gundacker HM, Kim HT, Dewald GW, Kantarjian HM, Pierce SR, Estey EH. The clinical spectrum of adult acute myeloid leukaemia is associated with core binding factor translocations. Br J Haematol. 2006;135(2):165-73. https://doi.org/ 10.1111/j.1365-2141.2006.06276.x
7. Al-Harbi S, Aljurf M, Mohty M, Almohareb F, Ahmed SO. An update on the molecular pathogenesis and potential therapeutic targeting of AML with t (8; 21)(q22; q22. 1); RUNX1-RUNX1T1. Blood advances. 2020;4(1):229-38. https://doi.org/10.1182/bloodadvances.2019000168
8. Raj TA, Gopinath P, Raj JG, Narayanan G, Nair SG, Philip DS, Raveendran S, Geetha P, Sreedharan H. Acute myeloid leukemia patients with variant or unusual translocations involving chromosomes 8 and 21–A comprehensive cytogenetic profiling of three cases with review of the literature. J Cancer Ther Res. 2022;18(3):697-703. DOI: 10.4103 /jcrt.jcrt_190_21
9. Gustafson SA, Lin P, Chen SS, Chen L, Abruzzo LV, Luthra R, Medeiros LJ, Wang SA. Therapy-related acute myeloid leukemia with t (8; 21)(q22; q22) shares many features with de novo acute myeloid leukemia with t (8; 21)(q22; q22) but does not have a favorable outcome. Am J Clin Pathol. 2009;131(5):647-55. https://doi.org/10.1309 /AJCP5ETHDXO6NCGZ
10. Rücker FG, Agrawal M, Corbacioglu A, Weber D, Kapp-Schwoerer S, Gaidzik VI, Jahn N, Schroeder T, Wattad M, Lübbert M, Koller E. Measurable residual disease monitoring in acute myeloid leukemia with t (8; 21)(q22; q22. 1): results from the AML Study Group. Blood, Am. J. Hematol. 2019;134(19):1608-18. https://doi.org/10.1182 /blood.2019001425
11. Foucar K, Hsi ED, Wang SA, Rogers HJ, Hasserjian RP, Bagg A, George TI, Bassett Jr RL, Peterson LC, Morice WG, Arber DA. Concordance among hematopathologists in classifying blasts plus promonocytes: a bone marrow pathology group study. International Journal of Laboratory Hematology. 2020;42(4):418-22. https://doi.org/10.1111/ijlh.13212
12. Suguna E, Farhana R, Kanimozhi E, Kumar PS, Kumaramanickavel G, Kumar CS. Acute myeloid leukemia: diagnosis and management based on current molecular genetics approach. Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders). 2018;18(3):199-207. https://doi.org/10.2174/1871529X18666180515130136
13. Li X, Liu G. Acute Myeloid Leukemias with Variant RUNX1:: RUNX1T1: Report of Three Cases. Hematop.2023;8(1). https://journals.librarypublishing.arizona.edu/hemepath/article/id/5668/
14. Vasu S, Kohlschmidt J, Mrózek K, Eisfeld AK, Nicolet D, Sterling LJ, Becker H, Metzeler KH, Papaioannou D, Powell BL, Kolitz JE. Ten-year outcome of patients with acute myeloid leukemia not treated with allogeneic transplantation in first complete remission. Blood adv. 2018;2(13):1645-50.https://doi.org/10.1182/bloodadvances.2017015222
15. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, Estey EH, Dombret H, Chevret S, Ifrah N, Cahn JY. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomized controlled trials. Lancet Oncol. 2014;15(9):986-96. https://doi.org/10.1016/S1470-2045(14)70281-5
16. Butler E, Ludwig K, Pacenta HL, Klesse LJ, Watt TC, Laetsch TW. Recent progress in the treatment of cancer in children. CA: a Cancer Journal for Clinicians. 2021;71(4):315-32. https://doi.org/10.3322/caac.21665
17. Wilde L, Cooper J, Wang ZX, Liu J. Clinical, Cytogenetic, and Molecular Findings in Two Cases of Variant t (8; 21) Acute Myeloid Leukemia (AML). Front Oncol. 2019;9:1016. https://doi.org/10.3389/fonc.2019.01016
18. Kim KH, Kim TG, Han JY, Kim JM, Kim JS, Kim HJ, Lee YH, Lee EY. Cytogenetical, Morphological, and Immunophenotypical Characteristics of Myeloid Myeloid Malignancies with t (8; 21). Korean J Hematol. 1999;34(1):18-26.
19. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, Wheatley K, Harrison CJ, Burnett AK, National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood, Am. J. Hematol. 2010;116(3):354-65 https://doi.org/10.1182/blood-2009-11-254441
20. Lin P, Chen L, Luthra R, Konoplev SN, Wang X, Medeiros LJ. Acute myeloid leukemia harboring t (8; 21)(q22; q22): a heterogeneous disease with poor outcome in a subset of patients unrelated to secondary cytogenetic aberrations. Mod Pathol. 2008;21(8):1029-36. https://doi.org/ 10.1038/modpathol.2008.92

Case Report **Open Access**

Unraveling Ovarian Fibroma: A Diagnostic Journey in an Infertile 38-Year-Old Women

Yasmeen Gul, Noman Sadiq, Nasrin Mumtaz

ABSTRACT

A 38-year-old woman approached with nine months of abdominal pain, discomfort, concerns regarding infertility therapy, and a history of laparotomy 3 years prior for suspected ectopic pregnancy. The patient has a history of normal menstrual cycles and a body mass index of 22. She was hospitalised for additional testing after a transvaginal ultrasound revealed a mass in the right ovary. Magnetic resonance imaging revealed a right ovarian multifocal fibrosing tumour with no ascites. The right ovary tumours were removed through a laparotomy, while at least half of the left ovary was saved for potential future fertility. Histopathology analysis of the tissue samples confirmed the presence of a right ovarian sex cord-stromal tumour. The presence of calcification in the fibroma and the presence of cells that lack mitotic activity, nuclear atypicality, or necrosis establish the diagnosis of ovarian fibroma. The patient did well following surgery and began menstruating normally at her one-month post-op checkup.

Keywords: Ectopic Pregnancy, Fibroma, Infertility, Ovarian Tumour.

How to cite this Article:
Gul Yasmeen, Sadiq N, Mumtaz N. Unraveling Ovarian Fibroma: A Diagnostic Journey in an Infertile 38-Year-Old Women. J Bahria Uni Med Dental Coll. 2023;13(4):305-7 DOI: https://doi.org/10.51985/JBUMDC2023205

CASE DESCRIPTION

A 38-year-old woman who had a laparotomy three years prior for a ruptured ectopic pregnancy and had been experiencing abdominal pain and discomfort for the past nine months and was worried about undergoing infertility treatment presented to the gynaecology outpatient department. The patient gave a history of normal menstrual cycles. Her body mass index of 22. Ovarian cyst with complications is the initial provisional diagnosis. transabdominal ultrasound revealed a mass in the right ovary. a substantial adnexal tumour on her right side was detected by vaginal ultrasonography and Doppler, but her ovarian blood flow was unaffected. She was admitted for further evaluation. A solid mass, measuring 8 cm 6.5 cm, was clearly visible on the Right side of the pelvis during the MRI scan, suggesting that it was a hemorrhagic mass originating from the Right ovary. The patient consented to exploratory laparotomy and, if necessary, to surgically remove the ovarian tumour while preserving as much ovarian tissue as possible. Preoperative tests were performed in accordance with hospital protocol and showed no abnormalities: complete blood picture (Hb: 10.5 gm/dl, TLC: 6.500/mm3, and platelet count 284,000/mm3), liver (AST: 20 IU/l and ALT: 30 IU/l), kidney function tests (serum creatinine 0.9 mg/dl and blood urea nitrogen 18 mg) and normal PT/APTT and INR. Her tumour markers profile showed: CA-125 was 25 IU/ml, inhibin B was 55 pg/ml, and anti-Mullerian hormone was 1,5ng/ml. Moreover, she had normal levels of free beta-Chorionic Gonadotropin (beta-HCG), Alpha-Fetoprotein (AFP) and Carcinoembryonic Antigen (CEA). An exploratory laparotomy revealed an 8cm x 6.5cm solid ovarian tumour originating from the Right ovary. The left ovary was looking normal, but it was adherent to the uterus and gut, probably due to her previous surgery for ruptured ectopic pregnancy. adhesiolysis was performed. The uterus was looking completely normal. The lump on the right ovary was removed, but the left ovary was saved for fertility purposes The excised mass was sent for histopathology. The microscopic examination of mass showed intersecting and anastomosing bundles and fascicles of spindle cells without mitotic activity, nuclear atypia or necrosis, confirming the ovarian fibroma diagnosis. Immunohistochemical status was performed, which shows Inhibin [positive], Calretinin [focal positive], CD99 [positive] ASMA [negative], and Dessmin [negative]. The patient was discharged on the 3rd postoperative day first follow-up after one month of surgery. She has already experienced her menstrual period. Further, follow-up is scheduled every three months for the recurrence of the fibroma and the ovarian reserve markers.

Yasmeen Gul
Assistant Professor, Department of Gynaecology and Obstetrics Meer Jam Ghulam Qadar Teaching Hospital Hub, Lasbella, Balochistan
Email: yasgul19@gmail.com

Noman Sadiq *(Corresponding Author)*
Associate Professor, Department of Physiology
Mekran Medical College, Turbat, Balochistan
Email: Noman_sadiq89@yahoo.com

Nasrin Mumtaz
Assistant Professor, Department of Gynecology and Obstetrics
Jhalawan Medical College Khuzdar, Balochistan
Email: asadnasreen45@gmail.com

Received: 29-05-2023
Accepted: 18-09-2023

Figure A: Low power view of cellular fibroma composed of intersecting fascicles of spindle cells

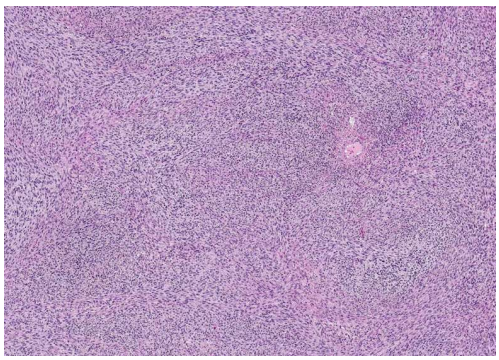
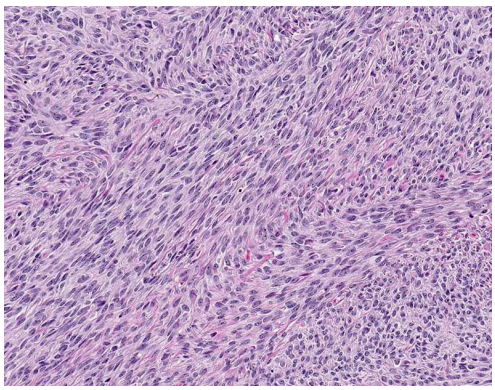


Figure B: High-power view of spindle cells with no cytologic atypia



DISCUSSION:

About 7% of all ovarian tumors are found in the sex cord stroma, but this subtype of ovarian cancer is extremely rare. One per cent to four point seven per cent of all ovarian tumours are fibromas.[1] Most fibromas are endocrine-inactive because they are made up of spindle-shaped stromal cells that secrete a collagenous stoma.[2] Although fibromas are most common in women in their late reproductive years, they can develop at any age; however, they are extremely uncommon in patients younger than 30.[3] Thecoma-fibroma type tumours account for less than 2% of all paediatric ovarian masses, according to the literature.[4-5] Fibroma-type masses are extremely uncommon in children. The size of a fibroma can vary greatly. Small lesions are often asymptomatic, but ovarian torsion may cause pelvic discomfort or severe abdominal pain in women as they grow. In the classic Meigs' syndrome (hydrothorax, ascites, and benign ovarian tumour), fibromas can be misdiagnosed as cancer and usually disappear once the tumour is removed.[6] Ascites is a reliable indicator that the tumour size is growing. They are typically harmless, but malignant progression has been reported.[1] A 24-year-old woman with a 15-cm unilateral ovarian fibroma was successfully treated by Najmi et al. via laparoscopic resection with ovarian preservation. When the preoperative diagnosis is unclear, they concluded that either laparoscopically or laparotomy could be used to remove the ovarian fibroma.[7] Ovarian fibromas, though benign, require surgery for treatment. This procedure typically involves open surgical access and the removal of the ipsilateral adnexa. It is estimated that 2% of cases will experience a recurrence.[8-9] The best preoperative strategy for ovarian tumours is still based on clinical, ultrasonographic, and tumour marker data. Doppler Ultrasound Imaging is the preferred method of investigation. In order to better characterize and differentiate from other solid ovarian masses, CT and MRI are often necessary.[10] The recommended procedure is surgical excision followed by an intraoperative frozen section. It is advised to perform an immunohistochemical analysis to rule out other possible diagnoses. A pathologist can only confirm the final diagnosis of fibroma via histopathology of the resected sample.[11] In our case the histological analysis, revealed that our patient's tumour was a benign fibroma composed entirely of fibrous tissue. We spared one of our patient's ovaries considering her age and wish to conceive. She began menstruating unexpectedly soon after the operation.

CONCLUSION:

Due to the rarity and difficulty of making a diagnosis preoperatively, ovarian fibromas are typically diagnosed through surgical removal and subsequent histological examination. As more and more evidence of these tumours is revealed in the literature, the debate surrounding their existence must be put to rest through an up-to-date literature review. When treating adnexal tumours in young girls and women, fertility preservation should be considered.

Authors Contribution:
Yasmeen Gul: reviewed all the cases for inclusion, data collection, drafted this article
Noman Sadiq: conceptualized and supervised the study, reviewed all the cases for inclusion,
Nasrin Mumtaz: Data Collection

REFERENCES:

1. Adesina AM, Imaralu JO, Yusuf AO, Ajani MA. Calcified bilateral ovarian fibroma in a 15 year old female: case report and literature review. Int J Med Pharm Case Rep. 2019;12(1):1–7. DOI:https://doi.org/ 10.9734/ijmpcr/ 2019/v12i130099.
2. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours. 4th ed. Vol. 6. Lyon: IARC; 2014. pp. 44–56.
3. GUPTA A, PATHAK S. Bilateral Fibrothecoma: A Rare Case in Young Woman. J. Clin. Diagnostic Res. 2020;14(5):1-3.
4. Heo SH, Kim JW, Shin SS, Jeong SI, Lim HS, Choi YD, et al. Review of ovarian tumors in children and adolescents: radiologic- pathologic correlation. Radiographics. 2014; 34(7): 2039–2055. DOI:https://doi.org/10.1148/rg.347130144.
5. Reitere D, Maðinska M, Lîdaka L, Franckevièa I, Baurovska I, Apine I. Bilateral ovarian fibromas in a 15-year-old primary amenorrhea patient: a case report. Radiology Case Reports. 2022; 17(2): 368-72. https://doi.org/10.1016/ j.radcr. 2021. 11.002.

6. Khanduja D, Kajal NC. A case report on Meigs' syndrome and elevated serum CA-125: A rare case report. J Pulmonol Respir Res. 2021; 5: 031-033. DOI:https://doi.org/ 10.29328/journal.jprr.1001021.

7. Najmi Z, Mehdizadehkashi A, Kadivar M, Tamannaie Z, Chaichian S. Laparoscopic approach to a large ovarian fibroma: A case report. J Reprod Infertil. 2014;15:57–60.

8. Borukh E, Ilyaev B, Muminiy SN, Babayev M, Musheyev Y, Levada M. Ovarian Fibroma Presents As Uterine Leiomyoma in a 61-Year-Old Female: A Case Study. Cureus. 2023;15(3):1-3. DOI:https://doi.org/10.7759/cureus.36264.

9. Adesiyun AG, Ameh N, Umar-Sulayman H. Laparoscopic Management of Benign Ovarian Tumours. In Gynaecological Endoscopic Surgery: Basic Concepts. Cham: Springer International;2022.pp 147-152. DOI:https://doi.org/10.1007/978-3-030-86768-3_14.

10. Guo Y, Jiang T, Ouyang L, Li X, He W, Zhang Z, et al. A novel diagnostic nomogram based on serological and ultrasound findings for preoperative prediction of malignancy in patients with ovarian masses. Gynecol Oncol. 2021;160(3):704-12. DOI:https://doi.org/10.1016/j.ygyno.2020.12.006.

11. Bharti S, Khera S, Sharma C, Balakrishnan A. Unilateral primary ovarian leiomyoma masqueraded as ovarian fibroma: A histopathological diagnosis. J Family Med Prim Care. 2021;10(9):3494-99. DOI:https://doi.org/ 10.4103/jfmpc.jfmpc_2546_20.

Case Report Open Access

A Rare Case of High-Grade Intracholecystic Papillary Neoplasm in the Gallbadder

Aun Ali, Madeeha Shahid, Shazadi Neelum Agha, Hurais Malik, Sidra Farishta, Muhammad Hudaib

ABSTRACT:

Intracholecystic papillary neoplasm (ICPN) is a rare pre-cancerous lesion. We report a unique case of 52 years-old male who presented with chronic upper abdomen pain, the exact nature of pathology was found after cholecystectomy on histopathological examination that reveals non-invasive ICPN of the gallbladder, unfortunately involving the resection margin with high-grade dysplasia. Due to limited cases recorded globally, definitive guidelines on the management of ICPN are lacking. We suggest long-term surveillance in all cases of incidental ICPN.

Keywords: Intracholecystic papillary neoplasm of gallbladder (ICPN), Intraductal papillary mucinous neoplasm (IPMN), Intraductal papillary neoplasm of bile duct (IPNB).

How to cite this Article:
Ali A, Shahid M, Agha SN, Malik H, Farishta S, Hudaib M. A Rare Case of High-Grade Intracholecystic Papillary Neoplasm in the Gallbadder. J Bahria Uni Med Dental Coll. 2023;13(4):308-10 DOI: https://doi.org/10.51985/JBUMDC2023210

BACKGROUND

ICPN is described as a grossly apparent, intraluminal developing mass-forming tumour that is histologically lined by epithelia that exhibit papillary/villous lesions as well as tubular structures with fine fibrovascular stalks and little intervening stroma. In addition, the term "ICPN with stromal invasion" also refers to ICPNs that exhibit microscopically discernible stromal invasion without nodular sclerosing reaction in the wall. Rare precancerous lesions of gallbladder cancer include intracholecystic papillary-tubular neoplasms[1]. It was found in only 0.4% of gallbladder specimen[2]. The radiological properties of ICPN have not yet been firmly standardized due to their rarity. [3, 4].

Aun Ali
Professor, Department of General Surgery
Fazaia Ruth PFAU Medical College, PAF Base Faisal
Email: aunali_72@hotmail.com

Madeeha Shahid
Senior Registrar, Department of General Surgery
Fazaia Ruth PFAU Medical College, PAF Base Faisal
Email: madeeha_87s@hotmail.com

Shazadi Neelum Agha
Fellow of Surgery, Department of General Surgery
Jinnah Postgraduate Medical Centre
Email: drneelumagha@gmail.com

Hurais Malik
4th Year MBBS Student
Fazaia Ruth PFAU Medical College, PAF Base Faisal
Email: huraismali38@gmail.com

Sidra Farishta
4th Year MBBS Student
Fazaia Ruth PFAU Medical College, PAF Base Faisal
Email: sidrafarishta1799@gmail.com

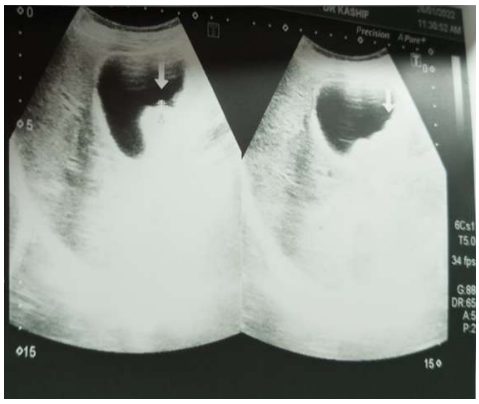
Muhammad Hudaib
4th Year MBBS Student
Fazaia Ruth PFAU Medical College, PAF Base Faisal
Email: hudaibtajamal@gmail.com

Received: 19-06-2023
Accepted: 20-09-2023

CASE PRESENTATION

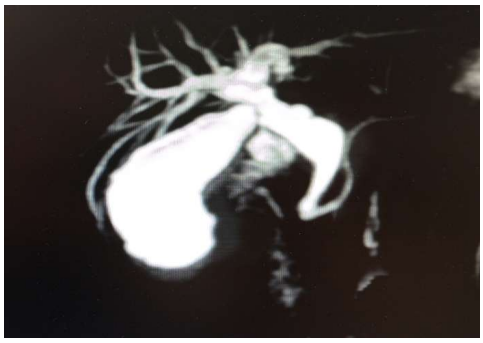
A middle-aged male patient aged 52 years presented at the outpatient clinic complaining of frequent right upper quadrant pain and nausea after heavy meals, which had worsened in the past 6 months, with no history of significant weight loss or anorexia. He is known hypertensive for which he has been taking amlodipine for the last 5 years. He had no prior surgeries or hospitalizations. No history of any addiction. He used to take a mixed diet. On examination, general physical examination and abdominal examination were unremarkable.

Figure 1: Upper abdominal ultrasound showed Polyps on the fundus measuring about 0.5x0.3cm.



His ultrasound abdomen was negative for cholelithiasis but revealed the gallbladder wall was slightly thickened approx. 0.4 cm. and irregular/polypoidal in appearance. A few polyps were seen largest one at the fundus measuring about 0.5 x 0.3cm (overall diameter of 1.5cm) and the proximal two-third common bile duct is dilated measuring about 0.7cm

Figure 2: Preoperative magnetic resonance cholangiopancreatography shows a Distended irregular thick-walled gallbladder and proximal CBD dilatation with distal tapering.



and distal CBD was narrowed. MRCP planned.

MRCP shows irregularly thickened wall gallbladder predominately region of body and fundus with tiny signal void foci. Mild dilatation of intrahepatic biliary channels, Common hepatic duct, and proximal CBD 7.8 mm with the abrupt reduction in caliber in distal CBD. Possibility of smooth stricture in the distal part of CBD. ERCP was not planned because there was no evidence of cholangitis or obstructive jaundice.

His liver function tests were normal, total bilirubin 16 umol/L (0-17umol/L), alkaline phosphatase 235 IU/l (65-270 IU/l), alanine aminotransferase 19 IU/l (0-42 IU/l).

His leukocyte count was also within the normal range.

He underwent laparoscopic cholecystectomy, which was difficult but done successfully. Cystic duct and artery clipped separately as shown in Figure 3.

Postoperatively patient develops acute hepatitis which was managed conservatively in the surgical ICU. The patient was discharged on the 9th postoperative day.

Incidentally, on histopathology, we found ICPN Type 1 biliary type with high-grade dysplasia extends to the margin of resection. Negative for invasive malignancy.Fig.5. Post-operative workup for the invasive disease was negative. Including, Ca19-9 was 33.38U/ml (<37U/ml), CEA was 1.13ng/ml (Smoker <5.Non-Smoker <3), AFP was 6.2 (<14.4 IU/ml). All results came out negative. CECT abdomen and pelvis demonstrate streaks of fluid around the liver. The small multi-septated intraperitoneal collection was noted. Intrahepatic ducts are mildly dilated. CBD is dilated (1.2cm) till its distal third where it abruptly reduces in caliber. Few enlarged necrotic lymph nodes are seen alongside the common iliac artery. A few prominent enhancing mesenteric lymph nodes were noted on the right hemi abdomen. See Figure 6.

We enrolled this patient into a surveillance program with 6 weekly Ca 19-9 levels and ultrasound abdomen, And after every three months, a Tri-phasic CT scan abdomen to evaluate gallbladder fossa mass.

Figure 3. Pre-operative image showing cystic duct and artery clipped separately

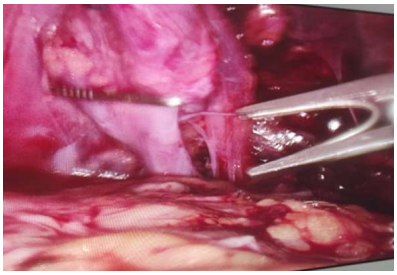


Figure 4: ICPN: Neoplastic growth with papillary pattern having fine fibrovascular stalks. Type 1 Biliary type with high-grade dysplasia.

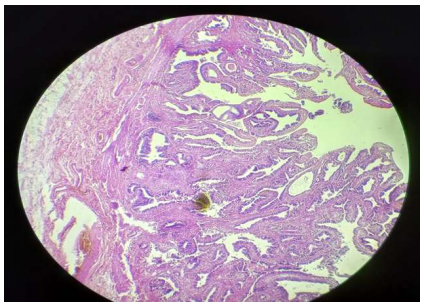
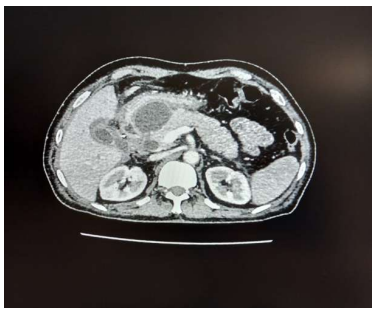


Figure 5: Contrast-enhanced CT abdomen (Sagittal image) showing Small intraperitoneal collection. Dilated proximal CBD. No gallbladder fossa mass



Recurrence was not reported at 14 months of follow-up.

DISCUSSION:

The World Health Organization initially provided a description of the relatively new entity ICPN in 2010[3]. For the characterization of several mass-forming precursor lesions, such as tubule-papillary adenomas, intestinal adenomas, papillary adenomas, and a few others, Adsay et al. suggested ICPN as a distinct pathologic entity in 2012[1]. ICPN is known as “Preinvasive adenocarcinoma of the gallbladder”. It is characterized by an intracholecystic papillary growth that may be connected to invasiveness. Invasive carcinoma is noted in 68 ICPN patients out of 123 that is 55% of ICPN patients, with a frequency of ICPN of less than 0.5%. [4]. Furthermore, about 50% of patients have no symptoms at all, and the features of ICPN are incidental during abdominal radiological investigations[4]. It is exceedingly challenging to distinguish ICPN from gallbladder

polyps and cancer in imaging investigations since their imaging findings are identical.

ICPNs are twice common in women[5] and approximately 0.5% of cholecystectomy specimens operated for symptomatic cholelithiasis or acute/chronic cholecystitis have them present. These lesions are all described as polypoid/papillary dysplastic neoplasms that manifest multifocal or diffuse growth on the mucosal surface of the gallbladder [6,10] most commonly involve body and fundus of gallbladder[9]. The cystic duct is a part of the gallbladder in the biliary system, not the extrahepatic bile duct. Additionally, a gallbladder cystic duct ICPN is incredibly uncommon but it is present in our case.[7]

These lesions also have a high rate of invasive malignant transformation and often show at least focal areas of high-grade dysplasia, with > 50% having an associated invasive carcinoma [6.]

ICPN is divided into four morphological subgroups, including biliary, oncocytic, gastric, and intestinal morphologies[8,9]. The most typical subtype is allegedly the biliary morphology[8] as in our case. In around half of all resected ICPNs, invasive cancer is discovered, especially in lesions with a mostly biliary architecture may have significant high-grade dysplasia.

These uncommon tumours frequently exhibit an intramucosal papillary or polypoid mass and mucin overproduction. IPMN and IPNB are thought to have certain traits in common with ICPN, although there are some differences as well [3].

The ICPN's natural history has not been thoroughly studied. After cholecystectomy, ICPN without aggressive cancer has a favourable prognosis. Those with pre-invasive ICPN have a 5-year survival rate of 78%, compared to those with invasive cancer, who have a 5-year survival rate of approximately 60%[11]. The overall survival outcome of ICPN is significantly better than that of ordinary-type gallbladder adenocarcinoma which is not associated with ICPN and has a 5-year survival rate of 18 to 30%[11]. Following the resection of both the ICPN and the IPMN, surveillance is required.

CONCLUSION:

A rare case of high-grade ICPN was incidentally discovered in 52-year-old male after laparoscopic cholecystectomy with a positive resection margin. A distinct pre-invasive neoplasm known as ICPN manifests as intraluminal mass lesions. As we previously noted, some patients will progress more aggressively metaplasia-dysplasia-carcinoma pathway, whereas some may do so via the more passive adenoma-carcinoma pathway[1]. Therefore, ongoing surveillance is advised.

Authors Contribution:
Aun Ali: Design, writing the final draft, data collection and analysis
Madeeha Shahid: Research conception, data collection and analysis
Shazadi Neelum Agha: Research conception
Hurais Malik: Data collection and analysis
Sidra Farishta: Data collection and analysis
Muhammad Hudaib: Data collection and analysis

REFERENCES:

1. Adamantios Michalinos, Alexandrou P, Alexandros Papalambros, Dimitrios Oikonomou, Sakellariou S, Evangelia Baliou, et al. Intracholecystic papillary-tubular neoplasm in a patient with choledochal cyst: a link between choledochal cyst and gallbladder cancer? World Journal of Surgical Oncology. 2016:2;14(1) . DOI 10.1186/s12957-016-0962-x
2. Faten Limaiem, Sahir Omrani, Hajri M, Seifeddine Baccouche. Bifocal intracholecystic tubulopapillary neoplasm: A rare and distinct tumor of the gallbladder. Clinical Case Reports. 2022 Mar 1;10(3) DOI: 10.1002/ccr3.5663
3. Yokode M, Hanada K, Shimizu A, Minami T, Hirohata R, Abe T, et al. Intracholecystic papillary neoplasm of the gallbladder protruding into the common bile duct: A case report. Molecular and Clinical Oncology. 2019 Sep 9; page 488-492 DOI: 10.3892/mco.2019.1919
4. Oh CH, Dong SH. Progression to invasive cancer after snare polypectomy of intracholecystic papillary neoplasms during gallbladder stone removal by percutaneous transhepatic choledochoscopy: a case report. BMC Gastroenterology. 2020 Nov 30;20(1) https://doi.org/10.1186/s12876-020-01547-x
5. Lograd A, Constantino J, Daniel C, Pereira J, Carvalho MT, Casimiro C. Low-Grade Dysplastic Intracholecystic Papillary Neoplasia: A Case Report. American Journal of Case Reports. 2021 Jan 23;22. DOI: 10.12659/AJCR.929788
6. Rowan D, Burcin Pehlivanoglu, Bahar Memis, Pelin Bagci, Ipek Erbarut, Nevra Dursun, et al. Mural Intracholecystic Neoplasms Arising in Adenomyomatous Nodules of the Gallbladder. The American Journal of Surgical Pathology. 2020 Oct 14;44(12):1649–57 doi:10.1097/PAS.0000000000001603
7. Oishi K, Ikeda M, Toyota K, Mandai K, Takahashi T. Intracholecystic Papillary Neoplasm Localized to the Cystic Duct: A Case Report. Case Reports in Gastroenterology. 2022 Feb 14; page 66–72. DOI: 10.1159/000522018
8. Watanabe Y, Naoki Mochidome, Nakayama H, Yoshitaka Gotoh, Taro Setoguchi, Shunya Sunami, et al. Intracholecystic papillary neoplasm associated with invasive carcinoma of the remnant gallbladder after subtotal cholecystectomy: a case report. Surgical Case Reports. 2022 Feb 21;8(1). https://doi.org/10.1186/s40792-022-01388-8
9. Yasuni Nakanuma, Nomura Y, Watanabe H, Tsuyoshi Takato, Sato Y, Kakuda Y, et al. Pathological characterization of intracholecystic papillary neoplasm: A recently proposed preinvasive neoplasm of gallbladder. Annals of Diagnostic Pathology. 2021 Jun 1;52:151723–3. https://doi.org/10.1016/j.anndiagpath.2021.151723
10. Wan X, Shi J, Wang A, Xie Y. Gallbladder papillary neoplasms share pathological features with intraductal papillary neoplasm of the bile duct. www.impactjournals.com/oncotarget/. Oncotarget, 2017, Vol. 8, (No. 19), pp: 31532-31539
11. Ryo Muranushi, Saito H, Matsumoto A, Kato T, Tanaka N, Nakazato K, et al. A case report of intracholecystic papillary neoplasm of the gallbladder resembling a submucosal tumor. 2018 Sep 27;4(1) https://doi.org/10.1186/s40792-018-0524-2

Letter to Editor **Open Access**

Robotic Surgery in Pakistan: Precision, Progress, and Challenges

Kanza Mehmood, Aakash Kumar

How to cite this Article:
Mehmood K, Kumar A. Robotic Surgery in Pakistan: Precision, Progress, and Challenges. J Bahria Uni Med Dental Coll. 2023;13(4):311
DOI: https://doi.org/10.51985/JBUMDC2023240

The Da Vinci Surgical (DVS) system, an example of surgery has made significant advancements since its introduction, in 2000. Thanks to state of the art technology surgeons are now able to perform procedures with exceptional precision and minimal invasiveness. These include urological, thoracic and cardiac surgeries, which have revolutionized the field of surgery. One major advantage of this robot is its ability to make incisions leading to reduced operative pain for patients fewer complications and faster recovery. It is important to note that robotic surgery should not be mistaken for robots; rather it empowers surgeons with control, over robotic arms that function as highly advanced surgical instruments.[1]

The robotic system comprises three essential components: the patient cart housing robotic arms, the vision cart equipped with camera and lighting controls, and the surgeon's console from where the surgeon directs the robotic arms. These components are interconnected via fiber optics, offering a seamless interface for the surgeon. Furthermore, this technology's potential extends beyond conventional surgery, with the possibility of telesurgery. Notably, the historic transatlantic surgery, Operation Lindbergh in 2001, demonstrated the feasibility of remote surgery using high-speed fiber optic connections. Telesurgery holds promise for addressing medical emergencies during long-duration space missions.[2]

Robotic surgery has witnessed a surge in utilization over the past few decades, particularly in colorectal surgery. The number of procedures performed with robotic assistance has escalated globally, with numbers surpassing 200,000 cases after 2007. It has revolutionized various medical disciplines, including urology, gynecology, general surgery, cardiothoracic surgery, and colorectal surgery. Surgeons in these fields have leveraged robotic assistance to enhance precision and patient outcomes.[3]

Robotic surgery adoption in Pakistan initially encountered difficulties but has advanced significantly. Institutions like Civil Hospital Karachi and The Sindh Institute of Urology and Transplantation have had success with more than 500 procedures, indicating the technology's potential to improve healthcare services in the area. Robotic surgery is being incorporated into the healthcare system, but there are cost obstacles to overcome. In countries with limited resources like Pakistan, public hospitals must carefully weigh the expenses of robotic surgery. While the private sector may offer a more economically viable option, it is essential to ensure equitable access to this advanced technology.[1,4]

Despite its advantages, robotic surgery presents challenges that warrant consideration. These include the potential for mechanical malfunctions, cybersecurity vulnerabilities, and prolonged surgical durations. Furthermore, the integration of artificial intelligence (AI) introduces complexities related to data security, ethics, and the impact on patient outcomes.[5]

In summary robotic surgery represents an advancement, in technology. It has the potential to improve care expand expertise and tackle healthcare challenges in remote or space constrained settings. To ensure its responsible implementation in countries like Pakistan it is crucial to establish regulations implement quality assurance protocols and raise awareness through campaigns. As we embrace the benefits of surgery we must also prioritize finding an equilibrium, between innovation and ensuring patient safety.

Kanza Mehmood
4th Year MBBS
Bahria University Health Sciences Campus, Karachi
Email: kanzamhd999@gmail.com

Aakash Kumar *(Corresponding Author)*
4th Year MBBS
Bahria University Health Sciences Campus, Karachi
Email: akashladkani@gmail.com

Received: 22-08-2023
Accepted: 19-09-2023

Authors Contribution:
Kanza Mehmood: Idea conception, write up
Aakash Kumar: Proof reading and final approval

REFERENCES:

1. Ullah K, Ochani S, Aaqil SI, Haider R, Nazir A. Current status and challenges of robotic surgery in Pakistan. Int J Surg. 2023;109(3).
2. Ghazanfar S. Robotic Surgery and its use in Pakistan. Vol. 13, Journal of the Dow University of Health Sciences. 2019.
3. Osofsky R, Kamya C, Hanif H, Phuoc V. A rare cause of lower gastrointestinal bleeding treated with robotic colorectal surgery. Surg Case Rep. 2021;7(1).
4. Ghazanfar S. Robotic Surgery and its use in Pakistan. J Dow Univ Health Sci. 2019 Aug 30;13:53–4.
5. Advanced Urology Institute. Advantages and disadvantages of robotic technology in urology. Advanced Urology Institute 2018. https://www.advancedurologyinstitute.com/advantages-disadvantages-robotic-technology-urology/ (accessed August 20, 2023).

Instructions to Author

The Journal of Bahria University Medical and Dental College abbreviated as JBUMDC is a peer reviewed quarterly multidisciplinary biomedical journal of basic and clinical health sciences. It accepts manuscripts prepared in accordance with the "Uniform Requirements for Submission of Manuscripts for Biomedical Journals, updated December 2015", adopted by International Committee of Medical Journal Editors (ICMJE) & PMDC guidelines for Medical & Dental journals. The Journal will encompass manuscripts from all fields of biomedical sciences in the form of Editorial (Invited/Editor), Original Article, Review Article (narrative reviews and systematic reviews), short communication, Commentary, case study, and letter to editor.

Peer Review Policy:

Every paper will be read by the editor and then will be sent to two reviewers, one internal and one external reviewer. If statistical analysis is included assessment by statistician will be carried out.

Plagiarism:

JBUMDC follows the ICMJE, PMDC and HEC guidelines. Each manuscript will be scrutinized. Plagiarism of the manuscript should be less than 18%.

Preparation of Manuscript:

Type the manuscript on ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 inch). Type or print on only one side of the paper. Use double spacing throughout the manuscript. Number pages consecutively, beginning with the title page. Put the page number in the lower right-hand corner of each page.

Contents of Manuscript for submission:

Submission items include a Covering letter, letter of undertaking duly signed by all authors, Ethical Review Committee (ERC) Letter, Author's declaration on JBUMDC template stating authors contribution, Title page and the Manuscript [Abstract, Key words, Introduction, Methodology, Results, Discussion, Conclusion, Acknowledgement, Authorship, Conflict of interest, References, Tables , Figures]**.** Title page should have complete title of the manuscript, along with the short running title, the names of all authors with qualifications, their department, affiliation, telephone number, e-mail, corresponding author, address for correspondence, short running title, source of funding (grant/equipment/drugs), number of figures and tables, total word count, total number of pages. Original manuscript should be of 2500 words excluding abstract and references and the references should be at least 20-25 for original study.

1. Abstract

It should have no more than 150 words for unstructured abstracts or 250 words for structured abstracts. The structured abstract should include:

1) Objective, 2) Study design and setting, 3) Methodology, 4) Result and 5) Conclusion.

[state the purpose of the study (objective), basic procedures (methodology with study design, subjects/animals, place & duration of study, drug/chemical/equipment, procedure or protocol), main findings (results) and conclusion (It should emphasize new and important aspects of the study.)]

Below the abstract provide, 3-10 key words that will assist indexers in cross-indexing the article. The key words should be in alphabetical order.

2. Introduction

State the purpose of the article and summarize the rationale for the study. Give only strictly pertinent references and do not include data or conclusions from the work being reported. At least 10 to 12 references should be included in the introduction. International and national literature review indicating the rational and objective of the study.

3. Methodology:

This section should include a statement indicating that the research was approved by independent local or regional or national review body(eg. Ethics committee, institutional review board) with ERC number. Clearly describe the type of study, selection of observational or experimental participants, including eligibility and exclusion criteria and a description of source population. Identify the age, gender and other characteristics of subjects. Mention the sample size and how it is calculated and the sample technique. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. For randomized clinical trials provide information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract. Describe statistical methods with enough detail to enable a knowledgeable person with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Define statistical terms, abbreviations, and most

symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

4. Results

Present your results in logical sequence in the text, tables, and illustrations according to the objective of the study. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Describe appropriate indicators of measurement error or uncertainty such as confidence intervals, P values. Report complications of treatment and dropouts from a clinical trial. Specify any general-use computer programs employed for analysis.

5. Discussion and Conclusion

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. Link the conclusions with the goals of the study.

6. Acknowledgment

List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

7. Authorship

Authorship credit is based only on the criteria laid down by International committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilibies/defining-the-role-of-authore-and-contributors. html).1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. 4) Agreement to be Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Conditions must be met. Authors should provide a description of what each contributed.

8. Conflict of interest

All authors have to disclose and submit any financial /personnel relationship that might bias and inappropriately influence their work.

9. References

Minimum 50% of the references must be from last five years. Local references must also be included. Vancouver style should be followed. Examples are:

a) Standard journal article

List the first six authors followed by et al. I) Less than 6 authors:

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreato-biliary disease. Ann Intern Med 1996; 1;124 (11):980-3

II) More than six authors:

Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12

b) Organization as author

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4

c) No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15

d) Chapter in a book

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh

JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78

e) Newspaper

Hasan Mansoor. Excessive use of drugs creating resistance to antibiotics. The Dawn 2013, 24 June; sect. Metropolitan (col.1-4)

10. Tables

Type or print out each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes. Explain in footnotes all nonstandard abbreviations that are used in each table. Identify statistical measures of variations, such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules.

11. Illustrations (Figures)

Figures should be professionally drawn and photographed. Photographic prints 127 × 173 mm (5 × 7 inches). Photomicro-graphs should have internal scale markers. Symbols, arrows, or letters used in photomicro graphs should contrast with the background. If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source

and submit written permission from the copyright holder to reproduce the material.

Legends for Illustrations

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units. Temperatures in degrees Celsius, Blood pressure in millimeters of mercury and all hematologic and clinical chemistry measurements in the metric system in terms of the International System of Units (SI).

Abbreviations and Symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Sending the Manuscript to the Journal

Submit manuscript by e-mail: editor.bumdc@bahria.edu.pk

All correspondence regarding submitted manuscripts will be via e-mail.

S No	Type of Article	Abstract type and word count	Key words	Total word count	References	Tables (Max)	Figures (Max)
1	Editorial	-	-	1000-1500	10-12	-	-
2	Review Article	Unstructured (150)	3-6	3000-3500	40-60	4	2
3	Original Article	Structured (250)	3-10	2500-3000	20-25	3	2
4	Medical Education	1. Original Structured (250)	3-10	2500-3000	20-25	3	2
		2. Review Unstructured (150)	3-6	3000-3500	40-60	4	2
		3. Reproducible work (guide lines, questionnaire)	Mention Source, Accessed on, Retrieval date				
5	Short Communication /Commentary/ Opinions/ Perspective	-	-	1200-1500	15-20	2	1
6	Student Corner	1. Original article Structured (250)	3-10	2500-3000	20-30	4	3
		2. Views/Perspectives/ Opinions Unstructured (150)	3-6	1200-1500	8-10	1	1
7	Case Report	Unstructured (150)	3-5	1200-1300	10-12	1	5
8	Letter to Editor	-	-	400-500	1-5	-	-

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC & PMDC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
ICMJE at https://www.icmje.org/journals-following-the-icmje-recommendations/#J
Bahira University DSpace Repository at http://111.68.99.22:8080/xmlui/handle/123456789/6388,
Pakistan Scientific and Technological Information Center (PASTIC) at http://pastic.gov.pk/

Journal of Bahria University Medical & Dental College

Published by Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA DHA Phase II Karachi, Pakistan
+92-21-35319491-9
http://jbumdc.bahria.edu.pk
editor.bumdc@bahria.edu.pk
https://www.facebook.com/jbumdc/, https://www.facebook.com/journal.bumdc.7