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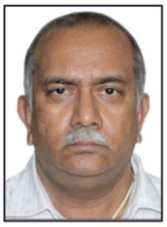

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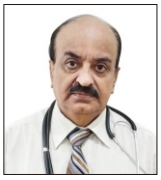
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# Contents

Editorial

# Postpartum Psychosis: A Global Public Health Crisis We Can No Longer Ignore

Motherhood is often associated with joy, love, and the promise of new beginnings. However, for some women, the postpartum period brings a severe and potentially life-threatening mental health crisis known as postpartum psychosis (PPP). Unlike the more widely recognized Postpartum Depression (PPD), postpartum psychosis is a rare but acute psychiatric disorder that can lead to hallucinations, delusions, confusion, and paranoia. It is estimated to affect 1 to 2 in 1,000 new mothers worldwide, yet awareness, early detection, and treatment remain inadequate across many healthcare systems.

The consequences of untreated postpartum psychosis can be catastrophic, leading to suicide, infanticide, family trauma, and long-term mental health deterioration. Despite its severity, PPP remains underdiagnosed and poorly understood in many parts of the world. Women experiencing symptoms often go unrecognized by healthcare providers, dismissed as having the “baby blues” or postpartum depression, resulting in delayed or absent intervention.

This article examines postpartum psychosis from a global public health perspective, emphasizing the urgent need for early screening, medical intervention, healthcare policy reforms, and community awareness. By addressing these issues, we can help prevent life-threatening complications and ensure that maternal mental health becomes a priority in public health strategies worldwide.

## Understanding Postpartum Psychosis :

Postpartum psychosis is a psychiatric emergency that typically develops within the first two weeks after childbirth, although symptoms can emerge within hours or days. Unlike postpartum depression, which is primarily characterized by sadness, exhaustion, and anxiety, postpartum psychosis includes severe mood disturbances, hallucinations, delusions and cognitive impairment.

## Symptoms of Postpartum Psychosis :

Extreme mood swings (euphoria followed by severe depression).

Delusions or false beliefs (eg, believing the baby is possessed or that they must save the world).

Hallucinations (hearing voices, seeing things that are not there).

Disorganized thinking and confusion.

Paranoia and extreme anxiety.

Insomnia or an inability to rest.

Agitation and impulsive behavior.

Suicidal thoughts or thoughts of harming the baby.

If left untreated, PPP can escalate rapidly, leading to dangerous behaviors. Studies suggest that women with postpartum psychosis are at a higher risk of suicide than the general population, and cases of infanticide linked to PPP highlight the urgent need for early detection and intervention.

## The Global Burden of Postpartum Psychosis

While postpartum psychosis occurs worldwide, awareness, diagnosis, and treatment vary significantly between countries. In high-income nations, maternal mental health is increasingly recognized as a critical component of healthcare, yet even in these regions, gaps in care exist. In low- and middle-income countries (LMICs), the situation is even more dire due to limited healthcare resources, stigma, and lack of specialized psychiatric care.

## Postpartum Psychosis in High-Income Countries

In countries such as the United States, Canada, the United Kingdom, and Australia, maternal mental health programs have improved significantly in recent years. **For example :**

The UK has implemented Mother and Baby Units (MBUs), where mothers with severe postpartum mental illnesses can receive inpatient care while staying with their babies.

The US has growing awareness of maternal mental health, yet postpartum psychosis screening is not standardized across healthcare systems, leading to inconsistencies in diagnosis.

Canada and Australia have launched public health campaigns to reduce stigma and encourage women to seek help.

Despite these advancements, many women still face barriers to care, including stigma, high healthcare costs, and lack of trained providers.

## Postpartum Psychosis in Low- and Middle-Income Countries (LMICs)

In many LMICs, maternal mental health is not a priority, and postpartum psychosis often goes undiagnosed or untreated.

**Some key challenges include :**

***Lack of mental health infrastructure* —** Many countries have limited psychiatric facilities, especially in rural areas.

***Cultural stigma* —** In some cultures, mental illness is associated with shame, weakness, or even supernatural beliefs, discouraging women from seeking help.

***Traditional healing practices* —** Some women are taken to spiritual or religious healers instead of receiving medical intervention.

***Gender disparities* —** Women in some societies have limited decision-making power over their health, leading to delays in seeking treatment.

A study conducted in India found that many cases of postpartum psychosis were misdiagnosed as possession by spirits, leading families to seek exorcisms instead of medical care. Similarly, in parts of Africa, mental illness is heavily stigmatized, leaving women with postpartum psychosis at risk of abandonment or violence.

The lack of data on postpartum psychosis in LMICs makes it difficult to assess the true burden, but public health initiatives must integrate maternal mental health services into existing healthcare systems to improve outcomes.

## Preventing Complications of Postpartum Psychosis

To reduce the risks associated with postpartum psychosis, a multi-faceted public health approach is essential. This includes early screening, timely medical intervention, improved healthcare policies, and community awareness.

### (1) Early Screening and Identification

Many cases of postpartum psychosis go undiagnosed due to a lack of routine mental health screening. To improve early detection:

Pregnant women should undergo mental health assessments during prenatal visits. Women with a history of bipolar disorder, schizophrenia, or previous postpartum psychosis should be considered high-risk.

Postnatal checkups should include mandatory mental health screenings at 1, 3, and 6 months postpartum to identify early symptoms.

Healthcare professionals should receive training to recognize the signs of postpartum psychosis, especially in primary care and obstetric settings.

**(2) Immediate Medical and Psychiatric Intervention**

Once symptoms of postpartum psychosis are detected, rapid intervention is crucial.

Emergency psychiatric care must be available in hospitals to ensure that women with severe symptoms receive immediate treatment.

Mother-Baby Psychiatric Units (MBUs) should be expanded globally to provide inpatient care without separating mothers from their infants.

Medication and therapy (such as antipsychotics, mood stabilizers, and cognitive behavioral therapy) should be made accessible and affordable for all mothers.

**(3) Strengthening Healthcare Policies and Support Systems**

Governments and healthcare systems must prioritize maternal mental health by:

Integrating postpartum mental health into primary healthcare services to make psychiatric care accessible to all women.

Providing paid maternity leave with mental health support, allowing mothers time to recover.

Establishing crisis helplines for women experiencing postpartum psychosis, offering 24/7 support.

**(4) Reducing Stigma and Raising Awareness**

The fear of judgment prevents many women from seeking help. To combat stigma:

Public health campaigns should educate communities about postpartum psychosis to normalize maternal mental health discussions.

Family education programs should encourage partners and relatives to support affected mothers.

Media and social platforms should feature real stories from survivors to reduce misinformation and encourage early intervention.

## Conclusion

Postpartum psychosis is a global public health crisis that remains underdiagnosed, misunderstood, and often neglected. While advancements have been made in high-income countries, low- and middle-income nations still face significant barriers to recognizing and treating PPP. The devastating consequences—suicide, infanticide, family trauma—are preventable with the right healthcare policies, early intervention, and societal support.

Addressing postpartum psychosis requires a global commitment to integrating maternal mental health services into existing healthcare systems, destigmatizing psychiatric illnesses, and ensuring that no mother suffers in silence. By making postpartum mental health a priority in public health agendas worldwide, we can save lives and improve the well-being of families across generations.

Hony Editor, JIMA **Kakali Sen**

Original Article

# A Study of Asthenopia among Medical Students in Digital Era

**Virinchi Chirravuri[1], Iqra Mushtaq[2], Shreeya Singh[3]**

**Abstract**

**Background :** The COVID-19 pandemic catalyzed a rapid shift from traditional classroom teaching to online learning, significantly impacting the education sector. This transition, particularly challenging for medical students reliant on practical training and patient interaction, also presented an opportunity to explore the potential of digital learning. With the widespread adoption of online teaching platforms in over 107 countries, digital learning emerged as a viable solution, connecting students and educators globally. This research investigates the prevalence of asthenopia, a condition associated with eye strain, among medical students during the COVID-19 era.

**Materials and Methods :** A cross-sectional observational study was conducted, involving 270 medical students using smartphones, laptops and computers. The study aimed to identify factors contributing to asthenopia, compare findings with pre-pandemic data, and provide guidelines for mitigating ocular health issues. Key findings revealed that digital device overuse was a significant factor contributing to asthenopia. The majority of students spent over four hours daily on screens with eyewear usage primarily attributed to excessive device use. Various preventive measures were employed, such as regular breaks and anti-glare glasses, though they did not consistently alleviate symptoms.

**Results :** Statistical analysis demonstrated that demographic factors, including gender and digital screen time, had limited influence on asthenopia prevalence. However, asthenopia was more common among students spending longer hours on digital devices. Comparing these findings with pre-pandemic studies underscores the increased prevalence of asthenopia among medical students in the COVID-19 era.

**Conclusion :** The rising prevalence of asthenopia among medical students highlights the need for proactive measures to protect ocular health. Strategies encompassing adequate sleep, dietary choices and improved mental well-being are essential. Public awareness campaigns, ergonomic practices and regular eye checkups should be encouraged to mitigate the adverse effects of digital device usage. This research contributes to our understanding of the post-COVID-19 impact on asthenopia and provides insights for targeted screening and awareness initiatives in the education sector.

**Key words :** COVID-19, Asthenopia, e-learning.

The COVID-19 pandemic severely impacted the education sector, forcing a sudden shift from physical teaching to blended online learning. This transition particularly affected medical students who heavily rely on practical training and patient interaction for their professional courses. However, amidst the challenges, the pandemic also presented an opportunity for digital learning to emerge as a solution. It accelerated the acceptance and adoption of online teaching, allowing students and teachers to connect virtually and explore various online educational platforms. These platforms offered courses from global institutions and industry players, bringing the world closer to students and promoting their growth as global citizens.

***Editor's Comment :***

- Asthenopia is highly prevalent among medical students due to excessive digital device use.
- Despite preventive measures, symptoms persist, highlighting the need for better awareness and ergonomic practices.

More than 107 countries had implemented a nationwide e-learning system by March, 2020[1]. Nevertheless, e-learning in higher education has progressively increased over the past two decades[2]. Digital learning can be described as a tool that can make the teaching and learning process more student centred, innovative, and flexible. However, the major aspects of e-learning that have been consistently explored are its usefulness and the learner's satisfaction. Several studies have shown that e-learning is mostly as good as traditional methods[3].

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Hence, being a boon to students, it helps them learn at their own pace even when they've been sequestered from their respective institutions, providing them a medium to learn and understand concepts. But, until recently little information is available regarding asthenopia with risk factors among the college students. Most of them have been experiencing the processing of functional maturation of the visual system in this time frame, which makes ocular tissue of college students more sensitive to the environmental change compared with other populations[4].

Asthenopia can manifest itself through a variety of perceptive symptoms such as off vision, dryness, redness, watering, itching in eyes, gritty sensation, impaired reading, light sensitivity, diplopia, headache[5]. These symptoms are frequently associated while they are doing near work for reading and writing whereby eye accommodative and vergence processes are more intense[6]. The prevalence of asthenopia is 46.3%[7,8]. The objectives of this study are to assess the occurrence of asthenopia among medical students, identify factors that contribute to its development, compare findings with pre-COVID-19 projects and provide necessary guidelines and precautions to mitigate ocular health issues.

## Materials and Methods

A cross-sectional observational study was conducted amongst medical students who are using smartphones, laptops and computers to determine the relationship between asthenopia and related risk factors amongst the medical students in the study period. The study was conducted at a tertiary referral hospital after taking the proper ethical committee clearance from the respective Institutional Ethical Committee.

Data is based on (1) demographics, (2) current major, (3) usage of digital device and time spent using it, (4) use of glasses or contact lenses, (5) symptoms of asthenopia and (6) preventive measures, will be collected by questionnaire. Our primary outcome of asthenopia is binary and its prevalence will be calculated. A bivariate analysis will be performed to correlate asthenopia with the different variables. A multivariate analysis will be conducted to determine the extent of the contribution of the different variables to asthenopia after controlling for confounding variables.

All the medical students willing to participate in the study and who are using a smartphone, laptop or computer and students not suffering from any ocular disease were included in this study. Students with amblyopia, conjunctivitis, eye inflammation/ infection, pre-existing medical conditions (arthritis, osteoporosis, thyroid disease, diabetes, hypertension, chronic migraine and chronic headache), strabismus, high myopia (more than -6.0 diopters), glaucoma or cataract, retinal nerve damage any eye disease, or history of eye surgery were excluded from the study. A convenient sampling was done while assuming a 95% confidence level with a 6% margin of error; the sample size came out to be 267 and was rounded off to 300.

The data was compiled and entered into an Excel sheet and analyzed by using an appropriate statistical test. Statistical analysis was done using SPSS Version 20.

A bivariate analysis will be used to assess the association between asthenopia and the following variables: demographics, digital device use and preventive methods. Age, being a continuous variable, was analysed using an independent t-test. Multiple logistic regression was performed to analyse the ones that contribute the most to asthenopia and control for the effect of confounding variables.

## Results

A total of 270 medical students participated in this study. Descriptive analysis indicated that almost 65% of the participants were females, while about 36% of them were males. Equal number of students were studying in 1st year (n=83; 30.74%) and 3rd year (n=83; 30.74%) of their course. Twenty-five percent of them were studying in the second year of graduation and 12.96% were studying in their fourth year. In 55% of them used eyewear only, while 12% used both glasses and contact lenses. However, about 35% were free of both glasses and contact lenses, indicating that majority of the students used eyewear as a result of the overuse of digital devices.

The possible risk factors of Asthenopia were examined as shown in Table 2. Majority of the students spent four to six hours on their devices per day. One-third of them spent more than 6 hours per day, about 20% of them spent two to four hours a day and very few spent less than two hours a day on their

devices. On an average, students spent more than four hours a day on digital devices.

Several preventive measures were taken by medical students to minimise the ill-effects of overuse of digital devices as shown in Table 1. More than 20% of them preferred to take regular breaks from screen time, 10% of them used anti glare glasses as well as took regular breaks, 10% used eye drops and frequent breaks from using devices and less than ten percent of the students used adjustable screens and also took frequent breaks. Other preventive measures used by students were adjustable screens, anti glare glasses, eye drop, regular break alone or a combination of these measures.

Multiple linear regression analysis was used to analyse the impact of different demographic factors on the frequency of Asthenopia presents the descriptive analysis of the various demographic factors (Table 2). Results showed that digital screen hours (Mean=3.07±0.81) had neutral influence on frequency of Asthenopia, eyewear (Mean=1.80±0.92), and dark room (Mean=1.46±0.71) had no influence on frequency of Asthenopia. A R2 value of 0.035 indicates that the demographic factors included were responsible for only 3.5% variation in the frequency of Asthenopia, suggesting that these factors did not contribute major changes to it (Table 3). The constant takes the value 2.36 and the predicted value of frequency of Asthenopia when the various demographic factors take the value zero. None of the factors including eyewear, digital screen time and dark room were found to be significant factors affecting the frequency of Asthenopia. Hence, they had no influence over it (Table 4).

Chi-square test was conducted to examine the association between different eyewear used by students and various demographic factors. The number of students who wore glasses compared to ones who use both glasses and contact lenses alternatively were drastically higher in regards to time spent in the dark room (Table 5). Moreover, there was a slight difference between the number of students who used glasses than those who didn't in terms of duration spent in the dark room. Despite these differences among the groups who use or do not use eyewear, the association between eyewear and duration of time spent in a dark room was found to be insignificant (Chi-square=7.736; p>0.05). The type of eyewear used and the duration of screen time were not significantly associated (Chi-square=10.699; p>0.05). Majority of them wore glasses compared to ones who used glasses as well as contact lenses and the ones who did not use any type of eyewear. However, these differences in the use of eyewear were found to be insignificant in terms of duration of digital devices used (Table 6).

Table 1 — *Frequency distribution of preventive measures adopted*

| Preventive measures adopted | Frequency (%) |
|---|---|
| Adjustable Screen | 10 (3.7%) |
| Antiglare glasses | 10 (3.7%) |
| Eye drop | 16 (5.93%) |
| Regular Break | 62 (22.96%) |

Table 2 — *Descriptive statistics*

| | Mean | STD Deviation |
|---|---|---|
| Gender | 1.64 | 0.48 |
| Eyewear | 1.80 | 0.92 |
| Digital Screen hours | 3.07 | 0.81 |
| Dark room | 1.46 | 0.71 |
| Length of years on screen | 3.19 | 1.29 |

Table 3 — *Model summary for impact of gender, eyewear, digital screen hours, hours spent in dark room with digital device and length of years on screen on Frequency of Asthenopia*

| R | R Square | Adjusted R Square | STD. Error of the Estimate |
|---|---|---|---|
| 0.186 | 0.035 | 0.016 | 0.370 |

Table 4 — *Impact of gender, eyewear, digital screen hours, hours spent in dark room with digital device and Length of years on screen on Frequency of Asthenopia*

| | Unstandardized Coefficients | | Standardized Coefficients | 't' | P value | 95.0% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | STD Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 2.361 | 0.141 | | 16.688 | 0.000 | 2.083 | 2.640 |
| Gender | 0.023 | 0.048 | 0.030 | 0.485 | 0.628 | -0.071 | 0.117 |
| Eyewear | 0.029 | 0.025 | 0.072 | 1.191 | 0.235 | -0.019 | 0.078 |
| Digital Screen hours | -0.045 | 0.029 | -0.097 | -1.530 | 0.127 | -0.102 | 0.013 |
| Dark room | -0.041 | 0.034 | -0.078 | -1.208 | 0.228 | -0.107 | 0.026 |
| Length of years on screen | -0.019 | 0.018 | -0.065 | -1.052 | 0.294 | -0.054 | 0.016 |

Table 5 — *Association between eyewear and dark room*

| Dark room | Eyewear | | | Total |
|---|---|---|---|---|
| | Glasses | Glasses, Contact Lenses | None | |
| < 2 Hours | 89 | 20 | 64 | 173 |
| | 60.5% | 64.5% | 69.6% | 64.1% |
| 2-4 Hours | 47 | 10 | 19 | 76 |
| | 32.0% | 32.3% | 20.7% | 28.1% |
| 4-6 Hours | 9 | 0 | 5 | 14 |
| | 6.1% | 0.0% | 5.4% | 5.2% |
| > 6 Hours | 2 | 1 | 4 | 7 |
| | 1.4% | 3.2% | 4.3% | 2.6% |

Chi-square = 7.736; p-value = 0.288

Table 6 — *Association between eyewear and digital screen*

| Digital screen | Eyewear | | | Total |
|---|---|---|---|---|
| | Glasses | Glasses, Contact Lenses | None | |
| < 2 Hours | 6 | 0 | 2 | 8 |
| | 4.1% | 0.0% | 2.2% | 3.0% |
| 2-4 Hours | 30 | 1 | 25 | 56 |
| | 20.4% | 3.2% | 27.2% | 20.7% |
| 4-6 Hours | 60 | 18 | 37 | 115 |
| | 40.8% | 58.1% | 40.2% | 42.6% |
| > 6 Hours | 51 | 12 | 28 | 91 |
| | 34.7% | 38.7% | 30.4% | 33.7% |

Chi-square = 10.699; p-value = 0.098

## Discussion

In the investigation conducted by Cheng-Cheng Han, Rong Liu,Ru-Ru Liu, Zhong-Hai Zhu, Rong-Bin Yu, and Le Ma on 500 students from five different universities in Xi'an, Shaanxi Province, China. They discovered a significant prevalence of asthenopia among college students in Xi'an, with a rate of approximately 57.0%. These findings suggest that college students are experiencing a decline in their eye health. Consequently, it is imperative to promptly identify the risk factors contributing to this condition and develop effective strategies to safeguard against asthenopia, ultimately enhancing visual function among college students[9]. Thus, asthenopia is a predominant problem among students, especially medical students. Therefore, the present study chose medical students suffering from eye-strain or asthenopia as the target audience.

Descriptive analysis indicated that almost 65% of the participants were females and about 36% of them were males. Almost 55% of them used eyewear only, 12% used both glasses and contact lenses and about 35% were free of both glasses and contact lenses, indicating that the majority of the students used eyewear as a result of the overuse of digital devices. In this study, students used either only one or a combination of these devices.

The possible risk factors of asthenopia were examined as shown in Table 2. A majority of the students spent 4 to 6 hours on their devices per day. One-third of them spent more than 6 hours per day and 20% of them spent two to four hours a day. Very few spent less than two hours a day on their devices. On average, students spent more than four hours a day on digital devices.

Several preventive measures were taken by medical students to minimise the ill-effects of overuse of digital devices as shown in Table 3. More than 20% of them took regular breaks from screen time. About 10% of them used anti glare glasses and took regular breaks, 10% used eye drops and frequent breaks from using devices. Less than 10% of the students used adjustable screens and took frequent breaks. Other preventive measures adopted by students included using an adjustable screen, anti glare glasses, eye drop, regular break singularly or a combination of these measures. Although in the present study, students reported taking different preventive measures, they complained of having different symptoms of asthenopia, suggesting that these preventive measures failed to reduce eye-strain among them.

None of the factors including eyewear, digital screen time and dark room were found to be significant factors affecting the frequency of asthenopia. However, it has been reported that longer duration of using devices on a daily basis increases the prevalence of asthenopia[10]. In addition, Ips, et al reported that the probability of children with eyestrain in using eyewear was higher compared to children who had no eye strain[11]. On the other hand, eye strain was significantly associated with the duration of digital device usage among school students. Additionaly, a difference between prevalence and frequency of asthenopia in terms of duration of time spent in front of digital screens has been reported[12].

Chi-square test was conducted to examine the association between different eyewear used by students and various demographic factors. The association between gender and the type of eyewear used was found to be significant. The association between eyewear and the duration of time spent in a dark room was found to be insignificant. The type of

eyewear used and the duration of screen time were not significantly associated. To the extent of our knowledge, this study is the first of its kind to report the relationship between eyewear used and demographic factors included in this study.

## Conclusion

Increasing prevalence of asthenopia among medical students and in general students owing to digital device abuse is of great concern to the society as it causes ocular complications, leading to poor attention and poor academic performances. Some of the factors that help in preventing asthenopia include adequate sleep, regular intake of vegetables, and a good mental frame play a crucial role in preventing asthenopia. Therefore, the prevalence of asthenopia is expected to be high among medical students because of their time-constrained lifestyle, responsibilities which require multitasking resulting in lack of rest and sleep and irregular intake of food[13,14]. This study examines the link between digital device usage and asthenopia prevalence among students. It aims to identify risk factors and fill the research gap regarding post-COVID 19 impact, providing insights for awareness campaigns and targeted screening efforts.Therefore, it is crucial to develop effective strategies to prevent asthenopia among students and improve their ocular health. Practices like inappropriate distance from digital screen, high brightness levels and their use before going to sleep. The public, especially students, should be made aware of the ill-effects of digital devices. Thus, decision-makers and stakeholders should ensure that the public are aware of necessary preventive measures; and should take efforts to implement better ergonomic practices and also encourage and conduct annual eye check-ups to ensure good health of the public.

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Original Article

# Patterns of Drug Resistance in Infections among Hemodialysis Patients: A Cross Sectional Study from a Tertiary Care Hospital of Eastern India

**Roshni Dandapat[1], Dipti Patnaik[2], Nipa Singh[3], Subhra Snighdha Panda[3], Kalpana Mund[4], Ankita Roy[5], Ashwini Prasad Pattnaik[6], Alpana Mishra[7], Basanti Kumari Pathi[3]**

## Abstract

**Background :** In patients undergoing hemodialysis, infection is the second most common complication following cardiovascular diseases. Antimicrobial resistance is spreading throughout the world and Multi Drug Resistant (MDR) organisms causing infection in this group of patients is also increasing. The main objective of the study was to to isolate the bacterial pathogens from various clinical samples collected from patients undergoing hemodialysis for more than 3 months and identify the drug resistant strains.

**Materials and Methods :** A cross-sectional study was conducted in the Department of Microbiology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar for a period of 2 years (November, 2020 to October, 2022). End Stage Renal Disease (ESRD) patients, age >20 years undergoing HD who developed symptoms and signs of inflammation at different sites like jugular catheters and Arteriovenous Fistula (AVF) after 48 hours of insertion were included. Blood, sputum, urine, swab from infected catheter site and catheter tips were collected aseptically and subjected for automated culture and sensitivity testing for bacterial pathogens.

**Results :** Among 150 cases included in the study, 43.3% patients had bacterial infections. Staphylococcus aureus (26.4%) was the commonest bacterial isolate from blood sample and Klebsiella pneumoniae was commonest among all other clinical samples. In 24% MDR bacterial pathogens were isolated from clinical samples and Klebsiella pneumoniae was the most common MDR Gram-negative bacterial isolate. Methicillin Resistant Staphylococcus Aureus (MRSA) was isolated in 8% cases. In 11% pathogens were Extended Spectrum Beta Lactamases (ESBL) producers and 5% were Carbapenamase producers.

**Conclusion :** Effective infection control strategy and hand hygiene should be carried out to decrease infections in HD cases.

**Key words :** Hemodialysis, Infection Control, Infection, Multi Drug Resistant.

Chronic Kidney Disease (CKD) is defined as the existence of kidney damage or an estimated Glomerular Filtration Rate (eGFR) less than 60 ml/min/1.73 $m^2$ that lasts for 3 months or longer, regardless of the etiology. It is divided into six stages depending on glomerular filtration rate, with stage G5 End Stage Renal Disease (ESRD) being the final and most severe[1]. So, renal replacement therapy like hemodialysis, peritoneal dialysis etc is required for their treatment. Settings where several patients receive hemodialysis simultaneously, there is numerous potential for the spread of infectious organisms as the technique necessitates vascular access for extended periods of time.

***Editor's Comment :***

- Effective infection control practices have to be to decrese the infections in hemodialysis patients. Also for any infection proper antibiotics have to administered according to the antimicrobial susceptibility report.
- Escalation or de-escalation of antibiotics need to be followed to prevent MDROs.

It has been shown that healthcare workers' hands or contaminated tools, supplies, injectable drugs, ambient surfaces or gadgets can transmit infectious pathogens from patient to patient. Patients receiving maintenance hemodialysis are more likely to contract an infection because uremia is known to increase the susceptibility of ESRD patients to infectious pathogens by impairing cellular immunity, neutrophil function, and complement activation.

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Infections are the second most common cause of mortality and hospitalization after cardiovascular disease among these patients[2]. When compared to the general population, HD patients had a 6.3-8.2 times higher yearly infection mortality risk[3]. Chronic dialysis patients are at risk of infections caused by nosocomial Multidrug Resistant (MDR) pathogens exhibiting decreased susceptibility to many antimicrobials[4]. MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories[5].

MDR organisms like Vancomycin Resistant Enterococci (VRE), Methicillin Resistant Staphylococcus Aureus (MRSA) and MDR Gram- negative rods are the predominant pathogens found in hemodialysis patients[6].

The majority of bacteremia incidents are linked to vascular access, particularly Central Venous Catheters (CVC). Coagulase negative Staphylococcus aureus and recently S aureus species resistant to Methicillin or Vancomycin (MRSA or VRSA) are the most common bacteria responsible for CVC associated bacteremia[7].

The primary aim of the study was to isolate and identify the bacterial pathogens in catheter tip, blood, swab from infected site, urine and sputum samples collected from patients undergoing hemodialysis for more than 3 months. The antibiotic susceptibility pattern of the isolated bacterial pathogens was observed for screening of the drug resistant strains.

## Materials and Methods

A prospective cross sectional study was carried out in the Department of Microbiology in association with Department of Nephrology of Kalinga Institute of Medical Sciences, Bhubaneswar between November, 2020 to October, 2022 which included all End Stage Renal Disease (ESRD) patients undergoing dialysis during this period. Total 150 ESRD patients were included and different samples like catheter tip, sputum, urine, peripheral venous blood and swabs were collected for screening of the bacterial pathogens.

### Inclusion Criteria :

ESRD Patients, age >20 years undergoing hemodialysis, who develop signs of inflammation at different sites like Jugular, Femoral, Subclavian catheters and AV fistula after 48 hours of insertion. Patients who develop fever, chills, headache, abdominal pain, diarrhea and hypotension and any other signs and symptoms suggestive of infection any time after 48 hours of insertion of central venous catheter during hospitalization and who have given their consent to participate in the study.

### Exclusion Criteria :

Patients who have fever, chills, headache and signs of inflammation within 48 hours of insertion of catheter or prior to dialysis, patients in whom blood culture was positive before dialysis and patients who have not given their consent to participate in the study.

### Sample Collection, Transport and Processing :

Catheter tip, swab from infected site of catheter, urine, sputum and peripheral venous blood were collected and processed as per the standard guidelines[8-11].

Peripheral venous blood were collected from two separate venepuncture sites (one from central line and one from peripheral line or both from peripheral lines) and incubated in BacT/ALERT (bioMerieux, USA). After the machine flagged bottle positive, the bottle was taken out and subcultured into Blood agar and MacConkey agar. Overnight incubation of plates was done at 37$^{o}$C in incubator[8-10].

Identification and antimicrobial susceptibility of isolates from all the samples were carried out with the Vitek 2 (bioMerieux, USA) system according to Clinical and Laboratory Standard Institute (CLSI) 2021 cut off points.Resistance detection was carried out using the advanced AES programme, which could identify and record resistance patterns utilizing MICs.

### Detection of ESBL and MRSA :

It was confirmed by standard disc diffusion method according to CLSI M100 2022[12].

Detection of Carbapenamase producer was done by modified Carbapenem Inactivation Method (mCIM) in conjunction with EDTA- modified carbapenem inactivation method (eCIM) according to CLSI M100 2022[12].

## Results

*Klebsiella pneumoniae*, *Staphylococcus aureus* (MSSA), *Staphylococcus aureus* (MRSA) *and Pseudomonas aeruginosa* were isolated from almost all the clinical samples. *Klebsiella pneumoniae* was the commonest aerobic bacterial isolate 32 (44.6%). *Staphylococcus epidermidis* 1 (0.6%) and *Staphylococcus hemolyticus* 9 (6%) were isolated only from peripheral venous blood.

From catheter tip, the bacterial pathogens isolated were *Klebsiella pneumoniae* (5%), *Acinetobacter baumannii* (3%), *Staphylococcus aureus (MSSA)*(3%), *Staphylococcus aureus (MRSA)*(3%) and *Pseudomonas aeruginosa* (1.6%). *Escherichia coli* 11

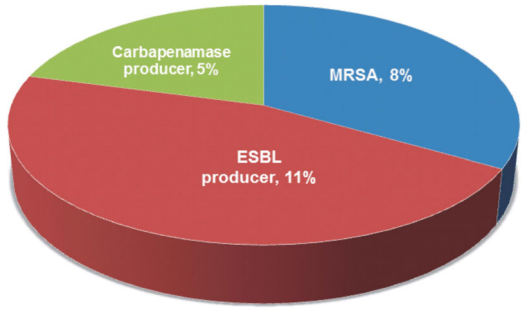


Fig 1 — *Drug resistant bacterial pathogens isolated from culture positive cases (n=104)*
MRSA: Methicillin Resistant Staphylococcus Aureus,
ESBL: Extended Spectrum Beta Lactamases

(12%) was the commonest isolate from urine sample.

Culture positivity of catheter tip was maximum by roll plate method 88 (58.7%) as compared to segment washing 28 (18.7%) which is also statistically significant.

Among the drug resistant bacterial pathogens isolated, Multidrug Resistant Organisms (MDRO) were commonest 25 (24%) followed by ESBL producers 12 (11%), MRSA 9(8%) and carbapenamase producers 4(5%)(Fig 1).

Isolation of ESBL producers were maximum from urine sample (10%) followed by sputum (2%) and peripheral venous blood (1.3%).

MRSA were mostly isolated from catheter tip (3.3%) followed by peripheral venous blood (2.6%), sputum (2%), swabs (1.6%) and urine (1%).

Carbapenamase producers were isolated from only peripheral venous blood sample (2.6%).

*Klebsiella pneumoniae* was the most common MDR Gram-negative bacterial isolate 10 (9%) from clinical samples followed by *Acinetobacter baumannii* 06 (5%), *Escherichia coli* 05 (4.8%), *Burkholderia cepacia* 03 (2.8%) and *Pseudomonas aeruginosa* 02 (1.9%)(Table 1).

Maximum susceptibility of MRSA isolates (100%) were seen for Daptomycin, Linezolid, Teicoplanin, Vancomycin and Nitrofurantoin. Resistance was maximum for Benzylpenicillin (100%). Susceptibility for Tigecycline, Gentamicin Cotrimoxazole and Erythromycin were 89%, 78%, 78% and 67% respectively. Least susceptibility was seen for Ciprofloxacin (44%), Clindamycin (44%) and Tetracycline (44%)(Fig 2).

Table 1 — *MDR Gram-negative bacterial pathogens from clinical samples showing culture positivity (n=104)*

| MDRO (Multidrug resistant organisms) | Percentage |
|---|---|
| *K pneumoniae* | 9% |
| *A baumannii* | 5% |
| *P aeruginosa* | 1.9% |
| *A denitrificans* | 00 |
| *B cepacia* | 2.8% |
| *E cloacae* | 00 |
| *E aerogenes* | 00 |
| *P mirabilis* | 0.9% |
| *E coli* | 4.8% |
| *E meningoseptica* | 00 |
| *Total* | 24% |

Maximum susceptibility of ESBL producers was seen for Ceftriaxone (59%). Amikacin, Cefepime, Cefoperazone+sulbactam, Gentamicin and Ticaracillin+clavulanic acid were susceptible among 58% isolates (Table 2).

Resistance to Amoxyclav, ampicillin, cefoperazone+Sulbactam and ceftriaxone was commonly seen among the MDR pathogens like *Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa* (Fig 3).

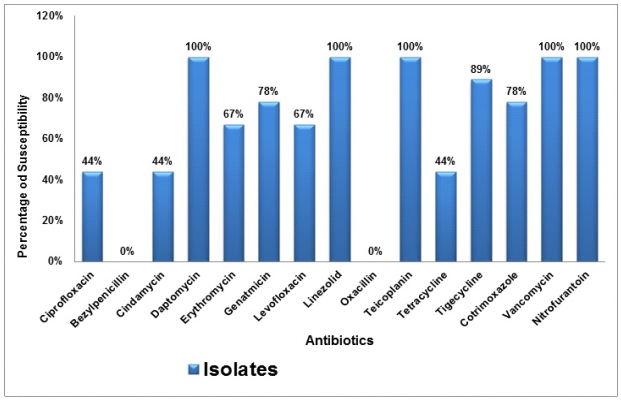


Fig 2 — Antibiotic Susceptibility pattern of MRSA (Methicillin resistant staphylococcus aureus) isolates

Table 2 — *Susceptibility pattern of ESBL producers*

| Drugs/ MDR | AK | AMC | AMP | CPM | CPS | CTR | CIP | CL | ERT | GEN | IPM | MRP | NIT | PIT | TGC | COT | DRP | TCC | FO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ESBL (12) | 58% | 50% | 41.7% | 58% | 58% | 59% | 50% | 16% | 41.7% | 58% | 41.7% | 41.7% | 55% | 33% | 33% | 41.7% | 41.7% | 58% | 55% |

ESBL: Extended spectrum beta lactamases, AK: Amikacin, AMC: Amoxcillin + Clavulanic acid, AMP: Ampicillin, CPM: Cefepime, CPS: Cefoperazone + Sulbactam, CTR: Ceftriaxone, CIP: Ciprofloxacin, CL: Colistin, ERT: Ertapenem, GEN: Gentamicin, IPM:Imipenem, MRP: Meropenem, NA: Nalidixic acid, NIT: Nitrofurantoin, PIT: Piperacillin + Tazobactam, TGC: Tigecycline, COT: Cotrimoxazole, CAZ: Ceftazidime, DRP: Doripenem, TCC: Ticacillin + Clavulanic acid , FO: Fosfomycin

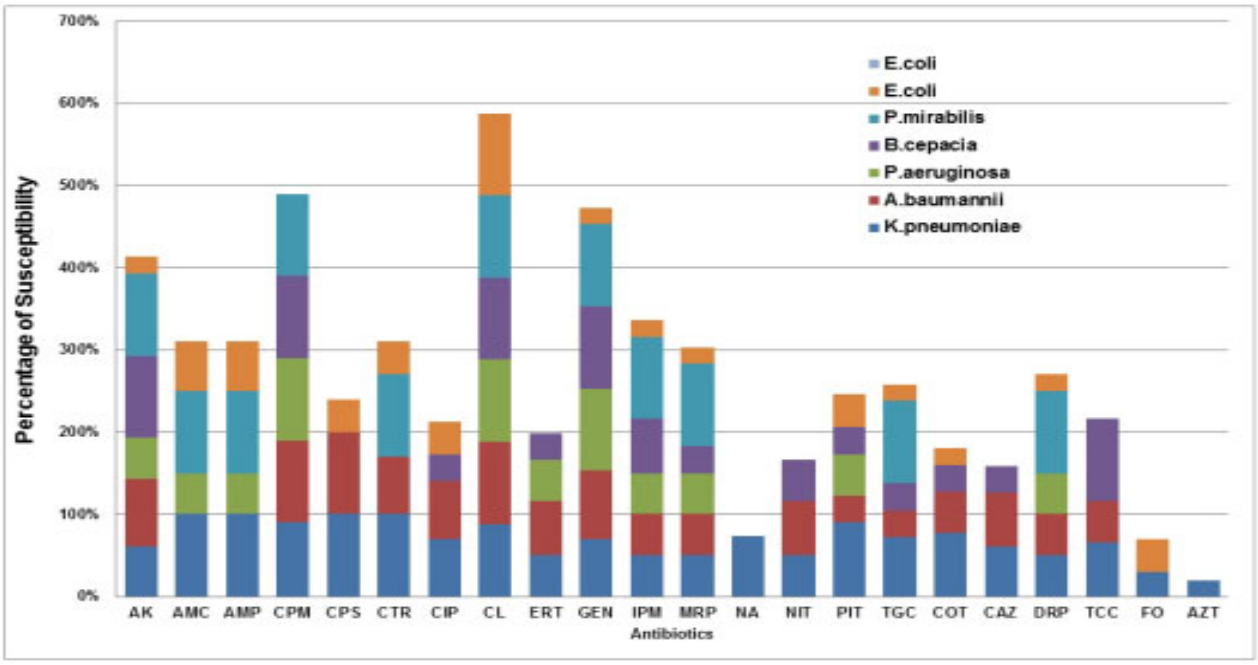


Fig 3 — Resistance pattern of MDR isolates

MDR: Multidrug resistant, AK: Amikacin, AMC: Amoxcillin + Clavulanic acid, AMP: Ampicillin, CPM: Cefepime, CPS: Cefoperazone + Sulbactam, CTR: Ceftriaxone, CIP: Ciprofloxacin, CL: Colistin, ERT: Ertapenem, GEN: Gentamicin, IPM:Imipenem, MRP: Meropenem, NA: Nalidixic acid, NIT: Nitrofurantoin, PIT: Piperacillin + Tazobactam, TGC: Tigecycline, COT: Cotrimoxazole, CAZ: Ceftazidime, DRP: Doripenem, TCC: Ticacillin + Clavulanic acid, FO: Fosfomycin

## Discussion

*Klebsiella pneumoniae* was the commonest aerobic bacterial isolate (44.6%) in our study followed by MSSA (16.3%), *Escherichia coli* (14%) and MRSA (10.2%). Our findings can be compared with the study carried out by Alzhami SM, *et al* (2019) where the common bacterial pathogens isolated were *Klebsiella pneumoniae* (40%), *Staphylococcus aureus* (16.7%), MRSA (9.1%) and *Escherichia coli* (3%)[13]. However, the study carried out by Fysaraki M, *et al* 2013 revealed *Staphylococcus aureus* as the commonest bacterial pathogen (36%) followed by *Staphylococcus epidermidis* (17%), *Escherichia coli* (9%) and *Klebsiella spp* (4%)[4].

Among the bacterial pathogens isolated from culture positive cases, multidrug resistant Gram-negative bacterial pathogens (MDRO) were commonest (24%) followed by ESBL producers (11%), MRSA (8%) and Carbapenamase producers (5%). Calfee DP, *et al* 2013 and 2015, in their study found MDRO (16%) as the commonest drug resistant bacterial pathogen followed by MRSA (1.4%-27%)[3,14]. Alzhami SM, *et al* 2019 also found 9.1% MRSA from hemodialysis patients[13]. AbuTaha SA, *et al* 2022 got MDRO 75.4% and ESBL 1.69% in contrast to our observations[15]. Fysaraki M, *et al* 2013 found 18% ESBL producers among the *Escherichia coli* isolates[4].

*Klebsiella pneumoniae* was the commonest MDR gram negative isolate and also the most common carbapenamase producer which is in contrast to the observations of Patel G, *et al* (2008)[16].

Among the Gram-negative bacterial isolates, *Klebsiella pneumoniae* was the most common multidrug resistant pathogen (9%) followed by *Acinetobacter baumannii* (5%), *Escherichia coli* (4.8%), *Burkholderia cepacia* (2.8%) and *Pseudomonas aeruginosa* (1.9%). Sahli F, *et al* 2016 found in their study *Klebsiella pneumoniae* strains (22.7%) as most common multidrug resistant strains followed by *Acinetobacter baumannii* (9.1%).

All the MRSA isolates[9] of our study were 100% sensitive to Daptomycin, Linezolid, Teicoplanin, Vancomycin and Nitrofurantoin and 100% resistant to Benzylpenicillin. But all *Staphylococcus strains*[8] were Methicillin resistant in the study carried out by Sahli F, *et al* 2016[17]. In 67% *Staphylococcus aureus* isolates and 68% *Staphylococcus epidermidis* showed resistance to Methicillin in the study carried out by Fysaraki M, *et al* 2013[4].

In our study maximum resistance was seen in *Proteus mirabilis* followed by *Klebsiella pneumoniae* and *Burkholderia cepacia*. Resistance was commonly seen for Cefepime, Colistin, Gentamicin and Amikacin, Ciprofloxacin Piperacillin+Tazobactam. Vicas AP, *et al* (2008)[18] found maximum resistance to ampicillin/sulbactam, ceftazidime, piperacillin/tazobactam and ciprofloxacin among the MDRGN bacterial isolates.

### Limitations of the Study :

The study involved a single hospital in one geographic area along with small sample size and thus represents single center experience. Isolation of bacterial pathogens from clinical samples could have been more but sometimes patients have received antibiotics prior to admission in the hospital as ours is a tertiary care hospital. We got the drug resistance pattern of the bacterial pathogens by phenotypic methods but could not confirm it by genotypic methods due to limited resources.

## Conclusion

This study involved a single hospital in one geographic area along with small sample size and thus represents single center experience. Isolation of microbial pathogens from clinical samples could have been more but some samples were processed after the antibiotic therapy as ours is a tertiary care hospital and sometimes patients have received antibiotics prior to admission in the hospital.

The rise of MDR species, particularly MRSA and ESBL-producing bacteria, makes infection management even more difficult. MDRO are responsible for a large number of infections in our patients. It is vital that health care providers should prevent these infections by implementing and enforcing infection control policies in hemodialysis centers, as well as administering appropriate antibiotic medication with restricted usage and duration.

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Original Article

# Comparative Study of Intra-articular Steroid Injection *versus* Prolotherapy in Regards to Improvement of Pain in Osteoarthritis of Knee Joint

**Suvadeep Bose[1], Sourav Dhar[2], Ashish Yadav[3], Arupjyoti Kurmi[4]**


## Abstract

**Background :** Osteoarthritis of the knee is one of the leading causes of pain, loss of function and decreased quality of life among adult rheumatological diseases. Osteoarthritis (OA) is a clinical syndrome of joint pain characterized by gradual loss of articular cartilage, osteophyte formation, subchondral bone remodelling, and inflammation of the joint[1]. When oral analgesic is ineffective, intra-articular (IA) injection (local corticosteroids, visco-supplements, platelet-rich plasma, prolotherapy) is another *non-operative modality* that can be performed[2,3].

**Aims and Objectives :** The present study was performed to assess the therapeutic effects of intra-articular dextrose prolotherapy on knee osteoarthritis and its comparison with intra-articular triamcinolone injection in terms of pain relief (VAS Score) and improvement in quality of life (WOMAC Score).

**Materials and Methods :** This prospective randomized study was conducted on patients visiting the OPD of NILD, Kolkata from March, 2020 to April, 2021. This study was performed on patients suffering from knee OA as a double-blind randomized clinical trial. One group received Prolotherapy (mixed with a local anesthetic- Lignocaine) and the other group received Intraarticular Steroid (mixed with a local anesthetic). Pre-procedural baseline assessment was done by VAS score and WOMAC score and compared it with the post-procedural improvement at 2nd, 4th and 6th week.

**Results :** Compared to pretreatment, both interventions caused significant improvement in pain (evaluated by VAS) and WOMAC (all its components) (all with P-value <0.005). At 2nd, 4th and 6th week post-procedure, pain reduction was significantly better in the corticosteroid group.

**Conclusion :** Both steroids (triamcinolone acetonide) and prolotherapy (25% dextrose) are effective as IA injections in the OA knee joint for providing pain relief, however, steroid is more efficacious than single session of prolotherapy. As both provide analgesia by different modes of action, a multimodal approach can be used to provide more complete analgesia with minimal side effects.


**Key words :** Osteoarthritis of the Knee, Steroids Injection, Prolotherapy, Local Anaesthetic.

Knee osteoarthritis (OA), also known as degenerative joint disease, is typically the result of wear and tear and progressive loss of articular cartilage. It is most common in elderly women and men. OA knee is a major source of disability worldwide owing to pain and loss of function [4]. It mostly involves weight-bearing joints of the body. Broadly it can be divided into primary and secondary Osteoarthritis. Primary osteoarthritis occurs in previously intact joints and is idiopathic. Secondary Osteoarthritis follows birth defects, dislocation, trauma and fracture, deformities and other diseases of joints or some systemic diseases. Synovial inflammation plays a critical role in the symptoms and structural progression of osteoarthritis[5].

Non-surgical treatment options include patient education, activity modification, physical therapy, weight loss, knee bracing, acetaminophen, NSAIDS, COX 2 inhibitor, corticosteroid injection and prolotherapy[6].

***Editor's Comment :***

- Both steroids (triamcinolone acetonide) and prolotherapy (25% dextrose) are effective as IA injections in the OA knee joint for providing pain relief, however, steroid is more efficacious than single session of prolotherapy. As both provide analgesia by different modes of action, a multimodal approach can be used to provide more complete analgesia with minimal side effects.

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Local Corticosteroids have been a mainstay in the treatment of osteoarthritis knee owing to their anti-inflammatory effects and immuno-suppressive effects. Clinically, it causes a decrease in erythema, swelling, heat and tenderness of the inflamed joints. It also leads to an increase in the relative viscosity of the synovial fluid with an increase in Hyaluronic Acid (HA) concentration[7,8].

Prolotherapy involves the injection of a small amount of an irritant substance (most commonly, hypertonic solution of dextrose) into synovial space. It is presumed to work by several mechanisms including a direct, osmotic, and inflammatory growth effect[9]. The hypothesized mechanisms for pain relief include stimulation of local healing among chronically injured extra- and intra-articular tissues, reduction of joint instability through the strengthening of stretched or torn ligaments and stimulation of cellular proliferation[10].

The aims and objectives of the study was to find the efficacy in remission of pain and duration of remission for (1) Prolotherapy, (2) Intra-articular steroid injection and (3) Compare between prolotherapy and intra-articular steroid injection.

## Materials and Methods

### Study Design & Population :

This prospective randomized study was done from March, 2020 to April, 2021 at National Institute for Locomotors Disabilities, Kolkata on patients visiting to the Outpatient Department. Total 60 knee joints with knee pain are divided into two groups by Group A and B with 30 knee joints in each group.

### Sample Size :

The formula used for sample size calculation was as follows : —

$n=4pq / (L^2)$

Where, n= required sample size,

p= 0.287 (as per the study by Pal CP, *et al*[135]),

q = 1 – p,

L = Loss % (Loss of information),

Here p= 0.287,

q=1-p = 1- 0.287 =0.713,

4pq = 4 x 0.287 x 0.713 = 0.81852

$L^2$ = 0.01364

L= 0.1167

Loss of information percentage = 11.67%

$n =4pq / (L^2)$ = 0.81852/0.01364 = 60.00 = 60

### Study Tool:

Numeric pain rating scale as per WOMAC pain score was used.

### Study Technique :

Cases were selected as per inclusion and exclusion criteria. The patients who fulfil inclusion and exclusion criteria will be approached with the proposal of the study. The aim of the study and procedure was explained and written informed consent was taken from patients, who agreed to participate. Thorough history and physical examination were done as per Study Performa.

All patients received conservative management, which included oral medications (paracetamol) and physical therapy, for the initial 3 months. Patients who were not cured were divided in two groups, group A and group B. A total of 60 patients with knee OA were randomly assigned into two groups by generating random numbers with MATLAB 2014b software, where even and odd numbers were attributed to corticosteroid injection and dextrose injection, respectively.Group A patients received prolotherapy and group B patients received intra-articular steroid injection.

The patients were assessed at baseline, 2$^{nd}$, 4$^{th}$ and 6$^{th}$ week after the procedure by a trained assessor (unaware of the injection process) using Visual Analog Scale of pain (VAS) and a Western Ontario and McMaster Universities Arthritis (WOMAC) questionnaire.

### Statistical Analysis :

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc, Chicago, IL, USA) and Graph Pad Prism version[5]. Data had been summarized as mean and Standard Deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. A Chi-squared test ($\chi^2$ test) is any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualifications, 'the chi-squared test' often is used as short for Pearson's Chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various t-tests are given below. In each case, the

formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a 't' value is determined, a p-value can be found using a table of values from Student's 't' - t-distribution. If the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.

p-value ≤0.05 was considered statistically significant.

## Analysis and Result

All continuous variables were presented as mean ±SD or median (1st Quartile, 3rd Quartile) as appropriate and compared between the groups by independent t-test for normally distributed data and by Mann-Whitney 'U' test for non-normal data. We have checked the normality of continuous data by the Shapiro-Wilk test. All qualitative data were presented as no.s and percentages of patients. The chi-square test or Fisher's exact test was used to see the difference between the groups for qualitative variables. All p-values <0.05 were considered as statistically significant.

Table 1 — *Demographic Details*

| | Group A | Group B | p-value | Test Used |
|---|---|---|---|---|
| No of Patients | 30 | 30 | | |
| Age (Years) | 49.17±8.52<br>Median 49<br>Range (36-65) | 52.27±9.13<br>Median 54<br>Range (37-69) | 0.18 | Independent sample t- test |
| Sex (Male/ Female) | 17:13<br>(56.7%:43.3%) | 20:10<br>(66.7%:33.3%) | 0.43 | Chi- square test |

Table 2 — *Age Distribution in Groups*

| Age Group (Years) | Group A | Group B |
|---|---|---|
| <40 | 6 (20%) | 3(10%) |
| 40-50 | 10 (33.3%) | 8 (26.67%) |
| 50-60 | 10 (33.3%) | 13 (43.33%) |
| 60-70 | 4 (13.33%) | 6 (20%) |
| Total | 30 | 30 |

Table 3 — *Association of Womac Pain scores and groups(pre-treatment)*

| Womac Score | Group A | Group B | P-value (Chi-square test) |
|---|---|---|---|
| 6 | 6(20%) | 7(23.3%) | 0.73 |
| 7 | 18(60%) | 15(50%) | |
| 8 | 6(20%) | 8(26.7%) | |
| Total | 30 | 30 | |

## Discussion

This prospective randomized study was conducted on patients visiting to the Outpatient Department of the National Institute for Locomotors Disabilities, Kolkata 700090 from January, 2020 to April, 2021. Total 60 knee joints with knee pain are divided into two groups. Group A and B with 30 knee joints in each group. Prolotherapy has been reported as a useful method in the treatment of chronic musculoskeletal and joint diseases. It is proposed that prolotherapy causes mild inflammation and cell stress in the weakened ligament or tendon area, releases cytokines and growth factors and induces a new healing cascade in that area, which leads to the activation of fibroblasts, generation of collagen precursors, and strengthening of the connective tissue[13].

### Group-A (Prolotherapy) :

Solution consisted of 5ml of 25% dextrose with 1 ml of lignocaine 2%.

### Group-B (Steroid) :

Solution consisted of 40mg(1ml) triamcinolone acetonide, 1 ml of lignocaine 2% and 4 ml sterile water.

It was observed that age and sex ratio (Tables 1 and 2) were comparable in two groups. Respective p-values were 0.18 and 0.43. Age in two groups were 49.17±8.52 and 52.27±9.13 respectively. There were 17(56.7%) and 20(66.7%) male patients in two groups respectively. We found that 38(63.3%) patients were under OA grade II and 22(36.7%) patients were under OA grade III.

Eslamian F, *et al*[11](2015) found that total WOMAC score and its subcategories showed a continuous improvement trend in all the evaluation sessions, so that at the end of the study, the total score decreased by 30.5±14.27 points (49.58%)(p<0.001). Improvements of all parameters were considerable until week 8 and were maintained throughout the study period.

Erdem Y, *et al*[12] (2020) found that clinical efficacy and pain were evaluated via the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at pre-treatment and one, three and six-month follow-ups. Intra-group statistical analyses revealed significant improvements in PrT+HA and PrT+DX groups for WOMAC and VAS scores compared with baseline.

Table 4 — *Womac pain scores at different period*

| Womac Score | Group A | Group B | P-value | Test used |
|---|---|---|---|---|
| Pre-treatment | 7±0.64<br>Median 7(7,7)<br>Range (6-8) | 7.03±0.72<br>Median 7(6.75,8)<br>Range (6-8) | 0.84 | |
| 2 Weeks | 5.03±0.76<br>Median 5(4,6)<br>Range (4-6) | 3.83±0.83<br>Median 4(3,4.25)<br>Range (2-5) | <0.0001 | Mann-Whitney 'U' test |
| 4 Weeks | 4.83±0.75<br>Median 5(4,5)<br>Range (4-6) | 3.53±0.9<br>Median 3(3,4)<br>Range (2-5) | <0.0001 | |
| 6 Weeks | 5.03±0.76<br>Median 5(4,6)<br>Range (4-6) | 3.8±0.96<br>Median 4(3,4.25)<br>Range (2-6) | <0.0001 | |

Fatimah N, *et al*[13](2016) found that 16.1 % showed 50% or more improvement in WOMAC score at 3 months post IASI therapy, whereas 38.7% of OA patients had more than 50% improvement in VAS score. Out of all factors, range of movement, local knee tenderness and radiographic score of the affected joint are the three parameters which can predict the improvement in WOMAC score after 3 months of IASI therapy (P = 0.013, P = 0.045 and P = 0.000, respectively).

Table 3 showing In Group A, 6(20%),18(60%) and 6(20%) patients had WOMAC pain scores of 6,7 and 8 respectively whereas in Group B, 7(23.3%),15(50%) and 8(26.7%) had those respective scores. There is no significant association between pain scores and groups (p=0.73).

Table 4 shows at 2 weeks after treatment, it was observed that the median WOMAC pain score was 5 and 4 respectively in the groups and there was a statistically significant difference between the groups (P-value <0.0001).

At 4 weeks after treatment, it was observed that the median WOMAC pain score was 5 and 3 respectively in the groups and there was a statistically significant difference between the groups (P-value <0.0001)

At 6 weeks after treatment, it was observed that the median WOMAC pain score was 5 and 4 respectively in the groups and there was a statistically significant difference between the groups (P-value <0.0001).

It was also observed that pain score was significantly reduced in both the groups but it was more reduced in the steroid group (Group B).

## Conclusion

It was concluded that both steroid (triamcinolone acetonide) and prolotherapy (25% dextrose) are effective as IA injections in OA knee joint for providing pain relief; however, steroid is more efficacious than prolotherapy. As both provide analgesia by different modes of action, a multimodal approach can be used to provide more complete analgesia with minimal side effects.

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**Conflict of Interest :** None

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Original Article

# Autonomic Neuropathy in Patients with Diabetic Peripheral Neuropathy: A Cross Sectional Study

**Meghana Shridhar[1], Poonam Ashok Kamath[2], Sudha Vidyasagar[3], Pallavi L C[4], Vijayendra Kedage[5]**

**Abstract**

**Aims and Objective :** The aim of our study was to estimate the proportion of autonomic neuropathy in Diabetes Mellitus patients with peripheral neuropathy. Our objectives were to perform cardiac autonomic neuropathy function tests. As a secondary objective we strived to determine the association of autonomic neuropathy with severity and different types of diabetic peripheral neuropathy and to determine prevalence of autonomic neuropathy in patients with hypoglycemia who present with neuroglycopenia.

**Materials and Methods :** In a cross-sectional study, 120 patients with diabetic peripheral neuropathy were selected. They were subjected to bedside testing for autonomic neuropathy. Patients who had resting tachycardia and significant postural hypotension were taken up for cardiac autonomic function testing in physiology lab.

**Results :** Out of 120 subjects, 109 had distal symmetric polyneuropathy, 9 had amyotrophy and 1 subject each had mononeuritis multiplex and mononeuropathy. Out of these subjects, 52% had resting tachycardia and 35% subjects had postural hypotension suggestive of autonomic neuropathy. 63.3% of subjects had autonomic neuropathy, out of which cardiac autonomic neuropathy was found in 41.7% subjects. In 30 patients had documented hypoglycemia out of which 23 had autonomic neuropathy. In 19 patients had neuroglycopenia out of which 17 had severe autonomic neuropathy.

**Conclusions :** There is a significant association between autonomic neuropathy and diabetic peripheral neuropathy. Hypoglycemia and neuroglycopenia patients were found to have higher predilection to develop autonomic neuropathy.

**Key words :** Cardiac Autonomic Neuropathy, Resting Tachycardia, Orthostatic Hypotension, Neuroglycopenia.

Diabetes is a disease with vascular repercussions. Of these, peripheral neuropathy is a well-studied microvascular complication, manifesting as Distal Symmetrical Polyneuropathy-sensory and motor (DSPN), plexopathy, mononeuropathy, mononeuritis multiplex and amyotrophy[1].

Various studies done in western population shows a lifetime prevalence of peripheral neuropathy of 50% in individuals with long-standing type 1 and type 2 DM[2]. Review of Indian literature revealed a study done by Darivemula, *et al* in rural areas of Andhra Pradesh, India, in 2017 showed a prevalence of 39.3%[3]. Another study done by D'Souza, *et al* in Mangalore, India in 2014 showed a prevalence of 32.2%[4]. This study used the Michigan scoring system to diagnose and stage peripheral neuropathy.

***Editor's Comment :***

- There is a significant association between autonomic neuropathy and diabetic peripheral neuropathy. Severe peripheral neuropathy can be associated with autonomic neuropathy. Also, hypoglycemia and neuroglycopenia patients have a higher predilection to develop autonomic neuropathy. Hence, detecting peripheral neuropathy and having a low index of suspicion for autonomic neuropathy can go a long way in reducing morbidity and mortality of patients with autonomic neuropathy.

Diabetic Autonomic Neuropathy (DAN) is a well-studied type of neuropathy that occurs due to an imbalance between the adrenergic and cholinergic systems[5]. It can have multisystem implications such as cardiovascular (cardiac autonomic neuropathy), gastrointestinal (gastroparesis, constipation, diarrhea), sudomotor (anhidrosis, non-healing foot ulcer) and genitourinary (cystopathy, sexual dysfunction)[6].

A cross sectional study done by Low PA, *et al* in Rochester, Minnesota, using Autonomic Symptom

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Profile (ASP) and Composite Autonomic Severity Score (CASS) showed the prevalence of DAN of 54% in Type 1 DM and 73% in Type 2 DM[7]. A study done in Maharashtra, India in 2017, estimated the widespread presence of autonomic affection upto 58% in patients with type 2 DM[8].

Cardiac Autonomic Neuropathy (CAN) is a grave complication of Diabetes Mellitus. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels which can affect heart rate and cause change in vascular dynamics[9]. CAN manifests as a spectrum, ranging from resting tachycardia and fixed Heart Rate to arrhythmias, severe orthostatic hypotension, and silent myocardial infarction[3]. Thus, it can lead to perilous sequelae.

A study done in western population showed that 50% of diabetic patients with diabetic polyneuropathy have asymptomatic CAN[7]. 100% of symptomatic CAN present classical peripheral neuropathy[10]. A study done by Shukla, *et al* in 2014 in Kanchipuram, Tamil Nadu, India using CAN function testing showed a prevalence of 53.2%[11]. In type 2 diabetes, the prevalence of CAN positively correlates with duration of diabetes and has been elaborated in up to 60% of patients with type 2 diabetes after 15 years[7]. In addition, CAN has been found detected in patients with pre-diabetes or metabolic syndrome[12].

Often, DAN can be asymptomatic yet lead to an adverse outcome. Unexpectedly high occurrence of sudden cardiorespiratory deaths during and after surgery in diabetics with evidence of DAN was observed in a study done by Care D, *et al*[13]. CAN is strongly associated with a 5-fold increased risk of cardiovascular mortality as per a metanalysis study done by Ziegler D[14]. Prevention of DAN will eliminate hypoglycemic unawareness and neuroglycopenia, especially in the elderly. Anticipating a high risk of DAN in patients with peripheral neuropathy is of great importance in reducing morbidity and mortality due to early screening and intervention. As far as we know studies to show relationship between DAN and peripheral neuropathy are very few.

This study was carried out to determine the prevalence of DAN in DPN and its clinical implications. As a secondary objective we tried to find a relation between DAN and patients with hypoglycemia who presented with neuroglycopenia.

## Materials and Methods

A tertiary care hospital based cross-sectional study was conducted among patients attending OPD or admitted in ward in between August, 2019 to August, 2021 meeting the inclusion-exclusion criteria. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of KMC (Kasturba Medical College) & Hospital, Manipal (IEC 580/2019). The study has been registered with Clinical Trials Registry of India (CTRI/2019/10/021742). Written informed consent was taken.

Sample size was calculated using the formula that, to estimate proportion of AN in DPN at 30% prevalence with 95% confidence level and relative precision of 20%, 233 DPN needed to be enrolled for the study. Only a proportion of subjects, ie, those with positive bedside CAN testing or symptoms of AN were to be subjected to CAN function testing. This was a time bound study and due to COVID -19 related restrictions, 120 subjects were recruited. Patients aged 18 years and above were asked questions based on a standard proforma regarding co-morbidities pertaining to diabetic peripheral neuropathy, hypoglycemia symptoms and autonomic symptoms. A thorough physical examination was done including anthropometry, pulse rate and Blood Pressure supine and standing. Laboratory investigations to diagnose diabetes and to rule out other systemic illness were done. Patients with history of drugs likely to confound analysis like beta blockers, clonidine, steroids, phenytoin, cisplatin, vincristine, amiodarone, fluoroquinolones, isoniazid were not included. Those suffering from diseases like chronic kidney disease, chronic liver disease, Human Immunodeficiency Virus infection, vitamin B12 deficiency, patients with severe systemic disease and unstable patients were excluded from the study.

Subjects were tested for peripheral neuropathy, according to the ADA guidelines 2017[1]

Michigan Neuropathy Screening Instrument (MNSI)[15] was used for scoring for assessment of neuropathy. In the patient history part, a score of $\geq$7 was taken as positive for the DPN. In the examination part, $\geq$8/10 was considered to be positive for the presence of DPN. Permission was obtained to use the scoring system which is attached.

Nerve Conduction Study (NCS) was done, using standard instruments and the severity and type of neuropathy (axonal/demyelinating) was determined.

Those in whom peripheral neuropathy was detected were included in the study. These patients were further tested for evidence of autonomic neuropathy.

### CAN Function tests were done (Bedside)[9] :

**Resting Tachycardia :** Heart Rate (HR) more than 100/min was taken as tachycardia

**Orthostatic Hypotension :** BP of the subject was taken while lying down quietly as well as when standing. The postural fall in BP after 3 min was recorded (Abnormal is a drop of >20mmHg systolic and/or >10mmHg diastolic BP after 3minutes of standing).

Further CAN function testing was done by Department of Physiology, KMC Manipal, in Patients with autonomic dysfunction symptoms, (or) Patients with abnormal bedside autonomic function testing (or) Patients with features of neuroglycopenia

Hypoglycaemic subjects were identified as per WHO definition[16], ie, those who presented with blood glucose <60mg/dL and symptoms of hypoglycaemia which resolved with glucose correction were included.

Neuroglycopenia patients were identified as hypoglycaemic patients who had additional symptoms[17] like abnormal mentation, anxiety, irritability, personality change, confusion, delirium, stupor, or coma. In our study, 30 patients had hypoglycaemia out of which 19 presented with neuroglycopenia.

### CAN Function Tests done by Department of Physiology, KMC Manipal :

**Deep Breathing HR Variability :** The subjects were requested to sit quietly and breathe deeply (10 s/ breath) for a total of 1 min. ECG was recorded consistently throughout the period. Points where each inspiration and expiration started was marked. The maximum HR when in inspiration(I) and minimum HR throughout expiration (E) in each breathing cycle were measured and expressed as mean for the six measured cycles as beats/min. E/I ratio was calculated. (Normal response >15 beats/min, borderline 11-14 beats/min; abnormal response <10beats/min[18]

**Immediate HR Response to Standing :** Subject was asked to lie comfortably on the bed and HR was recorded on an ECG machine. Then he was asked to stand up unaided and at that point a marking was done on the ECG. After this, the shortest RR interval at or around the 15th beat and largest RR interval at or around the 30th beat after starting was measured with a ruler. The HR response was expressed as 30:15 ratio (normal if >1.04; borderline between 1.01 and 1.03; and abnormal if <1)[18]

**Isometric Hand Grip Test :** The subject was asked to grip an inflated BP cuff using the hand of the dominant arm for a few seconds, for three times. The highest of the three readings (maximum voluntary contraction) was recorded. Subsequently, they were instructed to simply maintain handgrip and results were noted as the difference between the highest Diastolic BP (DBP) during handgrip exercise and the mean of three DBP readings before onset of handgrip (normal response >16 mmHg; borderline 11-15 mmHg; abnormal <10mmHg)[18]

**Valsalva Ratio :** The subjects were instructed to lie supine and then blow into a mouthpiece connected to a mercury sphygmomanometer and hold it at a pressure of 40 mmHg for 15seconds while ECG was recorded. ECG taken after this maneuver in lead II and V1 was observed and the ratio of the longest RR interval to the shortest RR interval was calculated (Valsalva ratio). Normal Valsalva ratio is >1.21 and values <1.2 were considered abnormal[18]

CAN positive subjects were graded as:

**Subclinical phase :** Decreased HR variability

**Early phase :** Resting tachycardia

**Advanced stage :** Exercise intolerance, orthostatic hypotension, cardiomyopathy with left ventricular dysfunction, silent MI

Analysis was done using SPSS software version 16. Continuous variables were demonstrated as mean and Standard Deviation (SD) or median. Discrete variables were expressed as percentages. P values were calculated to determine statistical significance.

## Results

### Baseline Characteristics (Table 1) :

### Clinical Profile of Hypoglycemia and Neuroglycopenia :

Among the 30 hypoglycemia patients, gender was distributed equally. 15 had resting tachycardia. 9 had postural hypotension. 23 subjects had features of autonomic neuropathy. 24 subjects had severe diabetic peripheral neuropathy.

Table 1 — *Characteristics of study population (n=120)*

| Characteristic | | Total (%) |
|---|---|---|
| Age (years) | 31 - 40 | 5(4.2) |
| | 41 - 50 | 20(16.7) |
| | 51 - 60 | 40(33.3) |
| | 61 - 70 | 31(25.8) |
| | Above 70 | 24(20.0) |
| Sex | Male | 74(61.7) |
| | Female | 46(38.3) |
| BMI (kg/m$^2$) | <18.5 | 5(4.2) |
| | 18.5 - 22.9 | 16(13.3) |
| | 23 - 24.9 | 28(23.3) |
| | ≥25 | 71(59.2) |
| Resting Heart Rate (beats/min) | <100 | 57(47.5) |
| | >100 | 63(52.5) |
| Postural Hypotension | Absent | 79(65.8) |
| | Present | 41(34.2) |
| HbA1C (%) | <6.5 | 6(5.0) |
| | >6.5 | 114(95.0) |
| FBS (mg/dl) | <140 | 17(14.2) |
| | >140 | 103(85.8) |
| PPBS (mg/dl) | <200 | 21(17.5) |
| | >200 | 99(82.5) |
| Neuroglycopenia | Present | 19(15.8) |
| | Absent | 101(84.2) |
| Hypoglycemia | Yes | 30(25.0) |
| | No | 90(75.0) |
| Neuropathy Type | Amyotrophy | 9(7.5) |
| | DSPN – mixed type | 94(78.3) |
| | DSPN – motor | 3(2.5) |
| | DSPN – sensory | 12(10.0) |
| | Mononeuritis multiplex | 1(0.8) |
| | Mononeuropathy | 1(0.8) |
| Neuropathy Symptom Severity | Absent | 6(5.0) |
| | Low | 24(20.0) |
| | Moderate | 55(45.8) |
| | High | 35(29.2) |
| Neuropathy Sign Severity | Absent | 22(18.3) |
| | Low | 61(50.8) |
| | Moderate | 33(27.5) |
| | High | 4(3.3) |
| Neuropathy Severity - Overall | Mild/Moderate | 28(23.3) |
| | Severe | 92(76.7) |
| Duration Of Diabetes (years) | <10 | 18(15.0) |
| | 10-20 | 34(28.3) |
| | >20 | 68(56.7) |
| Can Function Testing | Absent | 50(41.7) |
| | Subclinical | 7(5.8) |
| | Early | 57(47.5) |
| | Late | 6(5.0) |
| Autonomic Neuropathy | Present | 47(39.2) |
| | Absent | 73(60.8) |

Among the 19 patients presenting with neuroglycopenia, 12 were males and 7 were females. 12 had resting tachycardia and 7 had postural hypotension. 17 had severe autonomic neuropathy. 15 had severe peripheral neuropathy.

Autonomic Neuropathy and Clinical Profile : Among 76 autonomic neuropathy patients, 49 were males and 27 were females. 50 patients were diabetic for longer than 10 years. 46 subjects had poor glycemic control. 17 patients had neuroglycopenia.

### Diabetic Peripheral Neuropathy and Autonomic Neuropathy :

Among 76 patients with autonomic neuropathy, 65 had severe peripheral neuropathy, and it is statistically significant(p=0.003)

Among 76 patients with autonomic neuropathy, the most common type of peripheral neuropathy was found to be distal symmetric polyneuropathy (DSPN) (67 in number) in our study.

## Discussion

### Prevalence of Autonomic Neuropathy in Peripheral Neuropathy :

In our study, out of 120 diabetic peripheral neuropathy patients, 76 subjects had DAN. Hence prevalence of DAN in our study is 63.3%. In 14 subjects out of 19 neuroglycopenia subjects had DAN, prevalence being 73.7%.

Ahmed, *et al* in 2001 in Saudi Arabia found that out of 48 DAN patients, 32 had peripheral neuropathy[16]. It was a cross sectional study which enrolled 120 subjects. However, the study design was different from ours in that the baseline population was DAN patients who were further tested for diabetic peripheral neuropathy.

Sukla, *et al* did a case control study in 2016, which enrolled 126 subjects, where 62 subjects had DAN (53.2% prevalence). In this study, all subjects underwent objective assessment and hence had a lower prevalence[8]. Our study included subjective data like assessment of symptoms of autonomic neuropathy as well.

SEARCH trial done in 2006, in United States was a cohort study which included 1646 patients out of which 252 were type 2 diabetes mellitus. 43 subjects had DAN (17% prevalence)[17]. However, in this study only heart rate variability was measured. Other objective measurements were not done as done in our study. Also, this study included only adolescent age group. DAN has been found to increase with increasing age[18], hence our study had a higher prevalence.

### Duration of Diabetes and Autonomic Neuropathy:

Our study had 68 subjects with duration of diabetes >20 years out of which 50 had DAN and the association was found to be significant (p=0.025), as summarised in Fig 2.

Seung-Hyun, *et al* did a cohort study in 2008 in South Korea which enrolled 1021 subjects. Odds ratio was found to be 1.15 for duration >15 years however it can be highlighted that duration of diabetes in their sample were equally dispersed[19]). Our study had most patients in the age group >20 years. Since our baseline population had peripheral neuropathy incidence of which is known to increase with age[20].

A cohort study done by Jaiswal, *et al* in 2006 in US included 252 subjects out of which 40 patients had duration of diabetes >10 years[21]. Only 5 had DAN and 35 did not have the same. This study showed a negative association however it could be slightly skewed as only adolescent age group was included, it is highly likely that older adults who would have peripheral neuropathy were missed.

DAN increases with duration of diabetes as various mechanisms[22] like metabolic damage of nerve fibers, neurovascular compromise, activation of the polyol pathway, increase in oxidative stress progressively increase with time.

### Glycemic Control and Autonomic Neuropathy :

Most of DAN patients had poor glycemic control however the association was not significant as at baseline to start with most patients had poor glycemic control. In our study, 70 subjects had poor glycemic control, out of which 46 had DAN. 44 subjects had fair glycemic control out of which 27 had DAN. 6 subjects had good glycemic control out of which 3 had DAN. The p-value, however, was not significant probably because at baseline most subjects had poor glycemic control, as is highlighted in Fig 2.

In 2010 Hoeldtke et al examined 37 individuals with recent onset diabetes and followed them up for 3 years. They concluded that oxidative stress causes increased incidence of DAN, similar to our study[22]. Wessells et al included 761 men with diabetes and followed them from 1983 to 1989. It was found that of the study subjects, 23% reported erectile dysfunction, which is one of the features of DAN[23].

It is well known that hyperglycemia is a major driving force for most of the complications of diabetes. High levels of blood and cytoplasmic glucose causes upregulation of various metabolic pathways that can cause increased oxidative stress, which can cause chronic tissue damage. Diabetic peripheral neuropathy being one of the microvascular complications of diabetes has been known to be more in patients with poor glycemic control.

### Type and Severity of Peripheral Neuropathy and Autonomic Neuropathy :

In our study 76 subjects had DAN. Also, out of this, 67 had DSPN type of neuropathy. The association of type of peripheral neuropathy and DAN did not come as significant due to small sample size and most subjects had DSPN type of peripheral neuropathy, as per Fig 3b.

It was observed that 90 had severe and 30 had mild to moderate severity of peripheral neuropathy. Among those with severe disease, most (65) had DAN whereas DAN was present in only 11 subjects with mild/moderate peripheral neuropathy. This association has come as statistically significant (p=0.003) and is shown in Fig 3a.

A cross sectional study done by Ahmed, *et al* in 2001 in Saudi Arabia included 120 subjects out of which 48 had cardiac neuropathy among which 32 had peripheral neuropathy[16]. However, the design of the study was such that initially the group of CAN was identified and among them testing for peripheral neuropathy was done.

There have been very few Indian studies which have tried to prove higher chance of developing DAN among peripheral neuropathy patients. As per detailed literature review, not many studies have been done that attempt to correlate type of peripheral neuropathy or severity of peripheral neuropathy with DAN.

Peripheral neuropathy and DAN can be postulated to be interrelated and predictable of each other due to common causative mechanisms.

### Cardiac Autonomic Neuropathy :

In our study, 73 had CAN. 63 had only resting tachycardia and 41 had only postural hypotension. We had included bedside testing ie, detecting resting tachycardia and postural hypotension and specific testing in physiology lab. Most studies that evaluated cardiac neuropathy focussed on measurement of only heart rate variability[19].

Damage to the autonomic fibres that innervate the heart due to neuropathy causes imbalance between sympathetic and parasympathetic system and can present as CAN[24].

### Hypoglycemia, Neuroglycopenia and Autonomic Neuropathy :

In our study, out of the 19 hypoglycemic subjects who presented with neuroglycopenia, 17 had DAN, and

this association was found to be significant, as highlighted in Fig 2, though our study may have overestimated DAN due to inclusion of resting tachycardia as one of the parameters.

A cross sectional study done by Hepburn, *et al* with 302 subjects in 1990 in London showed that out of 21 neuroglycopenia subjects, 14 had autonomic dysfunction[25].

DAN is a risk factor for developing neuro-glycopenia as it causes obliteration of standard epinephrine response to hypoglycemia[26]. The presence of DAN, however, further attenuates the epinephrine response to hypoglycemia in diabetic subjects after recent hypoglycemic exposure[27].

Until recently, diabetic peripheral neuropathy and DAN were considered as two separate entities and there are several studies that demonstrate risk factors in both in a separate manner. However, DAN can be potentially life threatening and may remain silent for several years leading to a grave outcome[18]. On the contrary, peripheral neuropathy is a thoroughly studied complication and routinely sought for while examining a patient of diabetes mellitus.

Hence it would be of real practical use if there was a relationship between peripheral neuropathy and DAN which would help in earlier diagnosis, identification of high-risk individuals, prevent neuroglycopenia, and hence overall can lead to a favourable outcome.

The value of CAN in diagnosing autonomic neuropathy cannot be overestimated[28]. Also, there are very few international and no Indian study which has tried to extrapolate peripheral neuropathy to DAN.

## Conclusion

Prevalence of DAN is 63.3% among subjects with diabetic peripheral neuropathy. CAN was found in 58.3% among subjects with diabetic peripheral neuropathy. DAN was more common in males than in females. Duration of diabetes is a significant risk factor in the development of DAN. Distal symmetrical polyneuropathy sensory type has the maximum predilection to develop into DAN. More the severity of peripheral neuropathy, the more the chance of developing DAN. Hypoglycemic patients who present with neuroglycopenia have significantly higher predilection of having DAN.

### Strengths of the Study :

The present study is among the few Indian studies that have studied autonomic neuropathy among diabetes mellitus patients with peripheral neuropathy. To the best of our knowledge, there have been very few Indian studies that have documented an association between autonomic neuropathy and type of diabetic peripheral neuropathy. There is also not much data available on the association of neuroglycopenia and autonomic neuropathy in our country.

### Limitations of the Study :

The study was cross sectional in design, hence participants could not be followed up for progression or new development of autonomic neuropathy or its manifestations.

**Conflict of Interest :** None

**Funding :** No funding was obtained for this study.

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Original Article

# Polytherapy *versus* Monotherapy for Real-World Patients with Major Depressive Disorder in India

**Saili Dharadhar[1], Amit Sharma[2], Sharmada Nerlekar[3], Alkesh Patil[4], Ashwini Mule[4], Sagar Karia[5], Disha Pandurangi[6]**

## Abstract

**Background :** Major Depressive Disorder (MDD) is one of the common mental disorders that affects millions of people Globally.

**Aims and Objective :** This study compared the efficacy and safety of polytherapy *versus* monotherapy in patients with MDD in India.

**Materials and Methods :** This real-world, prospective, observational study was conducted in India between May, 2021 and April, 2023. The primary endpoint was change in Hamilton Depression Rating Scale-17 (HAM-D 17) scores from baseline between the cohorts. Secondary endpoints included assessment of suicidal ideation/behaviour in patients over time.

**Results :** Among the total 268 patients, 91 patients were prescribed polytherapy and 177 were prescribed monotherapy. Mirtazapine (42.9%) was the most frequently prescribed adjuvant. While a reduction in HAM-D 17 scores was reported over time in both cohorts, the change in HAM-D 17 scores from baseline for the polytherapy cohort was significantly higher than the monotherapy cohort at all timepoints ($p<0.005$). While the Columbia-Suicide Severity Rating Scale scores were significantly higher in the polytherapy cohort compared to monotherapy at baseline ($p=0.004$), the scores in both cohorts reduced over time and were significantly lower in the polytherapy cohort at Week 8 ($p=0.011$). Similar observations were reported in the number of patients with suicidal ideation/behaviour. Insomnia (35.2%) and constipation (36.2%) were the most frequently reported adverse events, respectively.

**Conclusion :** This study demonstrated superior efficacy of polytherapy over anti-depressant monotherapy in reducing HAM-D 17 scores and improving suicidal ideation/behaviour in patients with MDD in India. The safety profile of both the cohorts was comparable.

**Key words :** Antidepressants, Clinical Research, India, Polytherapy, Real-world.

Major depressive disorder (MDD) is one of the common mental disorders that affects more than 300 million people globally[1,2]. It is a leading cause of disability, with residual disability observed even after symptom remission[3]. MDD is also identified as a risk factor for the development and worsening of comorbidities[4].

Anti-depressants are commonly used for the treatment of depression. Although some studies demonstrate statistically significant effects of anti-depressants compared with placebo, several other studies claim that the benefits of anti-depressants are minimal with low importance for the average patient[2].

***Editor's Comment :***

- Patients who received polytherapy demonstrated significantly higher reduction in HAM-D 17 scores from baseline compared to those who received monotherapy at each time point.
- The polytherapy cohort elicited significantly lower suicidal ideation/behaviour compared to monotherapy at Week 8, despite of having significantly higher C-SSRS scores than monotherapy at baseline.
- The overall frequency of AEs reported were comparable between the cohorts, and no new safety findings were observed in this study

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In addition to the high risk of Adverse Events (AEs) associated with such drugs[2], antidepressant therapy faces challenges of inadequate response and relapse in some patients[5].

The initial treatment for MDD recommended by the Indian Psychiatric Society (IPS) includes medications or/and psychotherapy based on thorough initial assessment of the patient[6]. However, In India, the prescription patterns for anti-depressants have known to deviate from the WHO recommendations[5] with under-prescription for people with moderate/severe depression, and over-over-prescription for people with mild depression or with no disorders[7].

Additionally, mental disorders substantially contribute to suicide-related deaths. India reports the highest number of suicides globally[8]. As per a study in India, the prevalence of suicidal ideation was found to be 83% in patients with MDD[9]. Some studies claim that anti-depressants can increase suicidal ideation. However, conclusive data on this topic is limited[10-12]. As suicidal ideation/behavior is associated with the presence of the disorder as well as its treatment modality, it is difficult to evaluate the reason for increase in suicidal tendencies post initiation of the therapy.

In the real-world, psychiatrists frequently combine additional drugs with the key anti-depressant to achieve faster remission, alleviate other symptoms, or treat relapsed patients. However, such polytherapy is not recognized as standard therapy globally[13] and has limited evidence on its efficacy and safety.

This prospective real-world study compared the efficacy and safety of polytherapy *versus* monotherapy in patients with MDD in India.

## Materials and Methods

### Study Design :

This real-world, observational, comparative, prospective study was conducted in Mumbai, Maharashtra, India between May, 2021 and April, 2023. Each patient was followed up for 8 weeks from the initial (baseline) visit. The study protocol was approved by the Institutional Ethics Committee (Registration number: ECR/ 266/ Lokmanya/ Inst/ MH/ 2013RR 16; Study approval number: IEC/40/21).

The study was conducted in accordance with the Good Clinical Practice, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2008. Informed consent was obtained from patients, or parents/legal guardians for children under the age of 18, for performing the study.

### Study Population :

Patients of all age groups were eligible to be enrolled into the study if they presented episode(s) of MDD, as diagnosed by the psychiatrist, had Hamilton Depression Rating Scale-17 (HAM-D 17) total score of ≥15 or a Clinical Global Impression-Severity of illness (CGI-S) score of ≥3. All the patients were divided into two cohorts for the purpose of evaluation. The polytherapy cohort consisted of patients who were prescribed ≥1 medication for the treatment of MDD and the monotherapy cohort consisted of patients who were prescribed a single antidepressant. Exclusion criteria consisted of patients with a current or past history of seizure disorder, bipolar disorder, schizophrenia, or brain injury.

### Study Therapy :

Patients who were prescribed more medications, either anti-depressant or other class of drugs specifically for the treatment of MDD were categorized into the polytherapy cohort. Patients who were prescribed with one anti-depressant without any concomitant medication for the treatment of depression formed the monotherapy cohort. The decision of prescribing polytherapy or monotherapy was made by treating psychiatrist based on individual needs and characteristics of the patients. The dose of the drugs was determined based on the clinical need. Patients were allowed to continue medication for general illness such as diabetes or hypertension.

### Data Collection :

Data were collected by the psychiatrists on a predefined case report form (CRF) during routine patient visits at Week 2, Week 4, Week 6 and Week 8 after the 1st visit.

### Outcomes :

The primary endpoint of the study was the change in HAM-D 17 scores between patients on polytherapy *versus* monotherapy. The secondary endpoints included the assessment of suicidal ideation/behavior between the cohorts using the Columbia-Suicide Severity Rating Scale (C-SSRS) scores and percentage of patients with suicidal ideation/behavior over time. Adverse events observed during the study were reported for both cohorts.

### Statistical Analysis :

The data were analyzed using Statistical Package for the Social Sciences (SPSS), version 26.0. Descriptive statistics for continuous data included n, mean, median, standard deviation and minimum and maximum values. Descriptive statistics for categorical data included n, frequency and percentage. Kolmogorov-Smirnov tests were performed on the actual data. As it did not satisfy the assumptions of normality ($p<0.05$ for both cohorts), the Mann-Whitney U test (non-parametric test) was used for comparison between the cohorts. All the tests were two-tailed and the significance level ($\alpha$) was set at 0.05.

## Results

Among the total 268 patients, 91 patients were prescribed polytherapy and 177 were prescribed monotherapy. At baseline, the mean HAM-D 17 scores of patients from the two cohorts were 25.8 (8.4) mg and 24.4 (6.6) mg, respectively. Table 1 summarizes the baseline demographic and clinical characteristics of the patients. There was no significant difference between the proportion of men, women, and the HAM-D 17 scores between the two cohorts at baseline.

Among 91 patients who received polytherapy, most frequent ad hoc agents were anti-depressants (Mirtazapine [42.9%], desvenlafaxine [17.6%]), nervous system stimulants (Armodafinil [13.2%], Modafinil [13.2%]), anti-convulsants (Oxcarbazepine [12.1%]), anti-psychotics (Aripiprazole [8.8%]) and drugs for the treatment of Parkinson's disease. Mirtazapine was the most frequently prescribed concomitant medication (42.9%). Details of the concomitant medications have been provided in Table 2.

### Efficacy Evaluation :

**Hamilton Depression Rating Scale-17 (HAM-D 17)**

The change in HAM-D 17 scores from baseline to Week 2, Week 4, Week 6 and Week 8 were compared between the two cohorts. For both cohorts, the change in HAM-D 17 scores from baseline increased over time. However, the change in HAM-D 17 scores from baseline for the polytherapy cohort was significantly higher than the monotherapy cohort at all timepoints ($p<0.005$) (Fig 1).

### Safety Evaluation:

**Suicidal Ideation/Behavior**

Columbia-Suicide Severity Rating Scale scores for patients in both the cohorts reduced over time. At baseline, the C-SSRS scores in the polytherapy arm were significantly higher than those in the monotherapy arm ($p=0.004$) and continued to be

Table 1 — *Baseline demographic and clinical characteristics of patients*

| | Polytherapy (n=91) | Monotherapy (n=177) |
|---|---|---|
| Age (years), mean (SD) | 43.7 (14.6) | 36.6 (11.8) |
| Sex | | |
| Male, n (%) | 49 (53.8) | 105 (59.3) |
| Female, n (%) | 42 (46.2) | 72 (40.7) |
| HAM-D 17 score, mean (SD) | 25.8 (8.4) | 24.4 (6.6) |
| C-SSRS score, mean (SD) | 2.4 (2.6) | 1.9 (5.3) |
| Patients with suicidal tendency/ ideation, n (%) | 57 (62.6) | 96 (54.2) |

C-SSRS, Columbia-Suicide Severity Rating Scale; HAM-D 17, Hamilton Depression Rating Scale-17; SD, standard deviation.

Table 2 — *Concomitant drugs prescribed for the treatment of MDD*

| Concomitant medication | Number of patients, n (%) (n=91) |
|---|---|
| Acetyl Carnitine | 3 (3.3) |
| Aripiprazole | 8 (8.8) |
| Armodafinil | 12 (13.2) |
| Bupropion | 2 (2.2) |
| Cariprazine | 3 (3.3) |
| Desvenlafaxine | 16 (17.6) |
| Imipramine | 2 (2.2) |
| Lamotrigin | 2 (2.2) |
| Lithium | 3 (3.3) |
| Mirtazapine | 39 (42.9) |
| Modafinil | 12 (13.2) |
| Opipramol | 1 (1.1) |
| Oxcarbazepine | 11 (12.1) |
| Paroxetine | 5 (5.5) |
| Pramipexole | 2 (2.2) |
| Prothiaden | 6 (6.6) |
| Ropinirole | 3 (3.3) |
| Valproate | 4 (4.4) |
| Vortioxetine | 1 (1.1) |

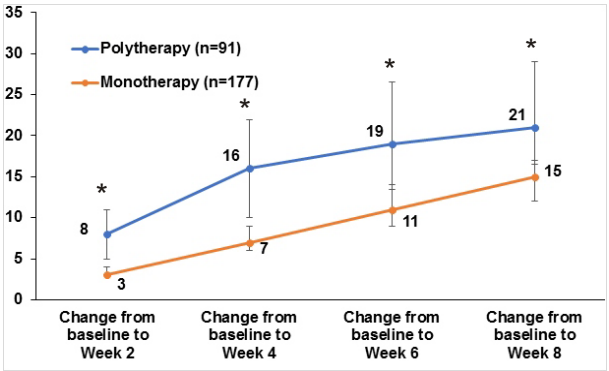


Fig 1 — Comparison of change in HAM-D 17 scores between cohorts at each time point

*p<0.005. HAM-D 17, Hamilton Depression Rating Scale.

significantly higher than the latter cohort up to Week 2 (p=0.001). At Week 4 and Week 6, there was no difference between the scores of the two cohorts. However, at Week 8, a significant difference was observed (p=0.011) between the two cohorts (Supplementary Table 1). As shown in Fig 2, scores of patients in the polytherapy arm which were higher than the monotherapy arm at baseline eventually reduced over time and were lower than the monotherapy arm by Week 8.

Similarly, there was a reduction in the number of patients with suicidal ideation/behavior over time in both the cohorts (Fig 3). At Week 8, the percentage of patients with suicidal ideation/behavior was lower in the polytherapy cohort compared to the monotherapy cohort.

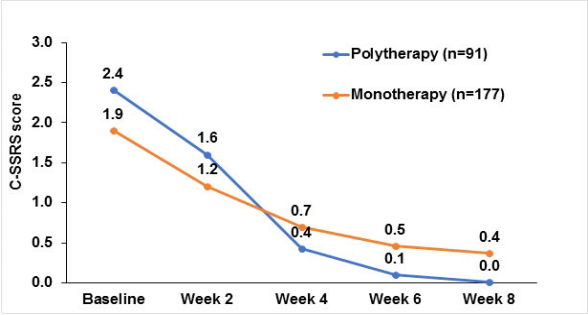


Fig 2 — Comparison of C-SSRS scores between cohorts at each time point
C-SSRS, Columbia-Suicide Severity Rating Scale.

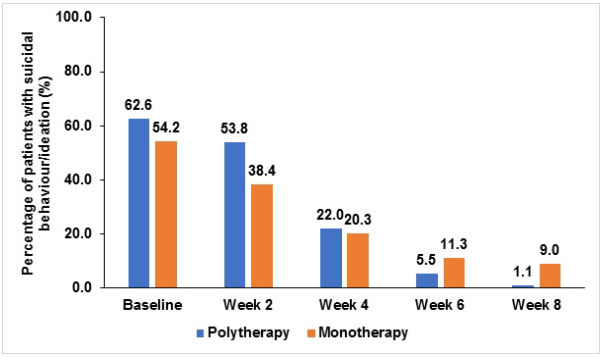


Fig 3 — Percentage of patients with suicidal ideation/behaviour over time

### Adverse Events (AEs)

Adverse events were reported by 78 (85.7%) and 167 (94.4%) of patients from the polytherapy and monotherapy arms, respectively during the study. Insomnia was the most frequently reported AE in the polytherapy cohort (35.2%) followed by nausea (34.1%). In the monotherapy cohort, the most frequently reported AEs were constipation (36.2%) followed by dry mouth (32.8%). Table 3 summarizes the AEs reported during the study. In addition to the solicited AEs listed in the CRF, two unsolicited AEs of irritability (n=1) and erectile dysfunction (n=2) were reported in the polytherapy cohort.

## Discussion

This study compared the efficacy of polytherapy *versus* monotherapy for patients with depression in India. Among all the participants enrolled in this study, 91 (33.96%) patients received polytherapy compared with 177 (60.04%) who received monotherapy indicating that polytherapy is less common in the Indian population. Among the ad hoc agents prescribed, most were psychotropic drugs, with antidepressants reported to be the most common. The reasons to add concomitant anti-depressants could be the high frequency of AEs caused by frequently prescribed antidepressants[14,15]. Adding antidepressants of a different class help target different mechanisms while that of the same class may help reducing the dose of the primary drug and thus reduce the frequency of AEs associated with it.

There have not been many studies comparing polytherapy and monotherapy for the treatment of MDD. Very few global studies involving combination therapies such as fluoxetine and desipramine[16],

Table 3 — *Number of patients with adverse events reported during the study in each cohort*

| | Polytherapy (n=91) | | Monotherapy (n=177) | |
|---|---|---|---|---|
| | n | % | n | % |
| Anxiety | 10 | 11.0 | 21 | 11.9 |
| Anorexia | 11 | 12.1 | 43 | 24.3 |
| Asthenia (Weakness) | 6 | 6.6 | 9 | 5.1 |
| Constipation | 9 | 9.9 | 64 | 36.2 |
| Decreased libido | 5 | 5.5 | 10 | 5.6 |
| Diarrhea | 4 | 4.4 | 22 | 12.4 |
| Dizziness | 8 | 8.8 | 19 | 10.7 |
| Dry mouth | 11 | 12.1 | 58 | 32.8 |
| Dyspepsia | 8 | 8.8 | 38 | 21.5 |
| Fatigue | 12 | 13.2 | 7 | 4.0 |
| Headache | 14 | 15.4 | 17 | 9.6 |
| Insomnia | 32 | 35.2 | 26 | 14.7 |
| Nausea | 31 | 34.1 | 41 | 23.2 |
| Somnolence | 6 | 6.6 | 32 | 18.1 |
| Upper abdominal pain | 7 | 7.7 | 15 | 8.5 |
| Vomiting | 12 | 13.2 | 4 | 2.3 |
| Giddiness | 2 | 2.2 | 0 | 0.0 |
| Irritability | 1 | 1.1 | 0 | 0.0 |
| Erectile dysfunction | 2 | 2.2 | 0 | 0.0 |

fluoxetine and other non-monoamine oxidase inhibitor anti-depressants[17], or selective serotonin reuptake inhibitors (SSRIs) with noradrenaline[18] have demonstrated rapid effect and considered to be effective strategies for non-responders and for treatment resistant depression. A real-world Japanese study demonstrated efficacy of adding Aripiprazole to regular anti-depressants using the Montgomery-Asberg Depression Rating Scale (MADRS)[19]. To our knowledge, this is the first study comparing polytherapy inclusive of multiple drugs with monotherapy for MDD in India. In this analysis, patients with polytherapy demonstrated significantly better improvement in HAM-D 17 scores. This difference was significant from Week 2 and continued up to end of the study indicating that addition of suitable psychotropic agents can help alleviate overall symptoms of depression faster, with notable difference observed as soon as 2 weeks after therapy initiation compared to monotherapy.

Apart from the general symptoms, suicidal thoughts are common in patients with depression[9]. Suicidal tendencies in patients with depression and on anti-depressant therapies has received considerable public attention. As suicidal ideation/behavior is also associated with the use of antidepressants[10,11,20], it is necessary to evaluate if combination therapy increases suicidal tendencies in patients. At baseline, patients in the polytherapy cohort had significantly higher C-SSRS scores than the monotherapy cohort. This difference between the cohorts reduced over time with no significant difference observed at Week 4 and Week 6. Surprisingly, at Week 8, C-SSRS scores in the polytherapy cohort reduced further and were significantly lower than monotherapy indicating a rapid and more robust decline in suicidal tendencies in patients who received polytherapy. A similar cross over observed in the percentage of patients with suicidal ideation/behavior confirms that polytherapy is more efficient in reducing suicidal thoughts compared to monotherapy. These findings are contradictory to the literature that states Mirtazapine, Venlafaxine and Trazodone are associated with the highest rates of suicide and attempted suicide or self-harm[21].

The incidence of adverse reaction to anti-depressants is considerable with the most common group of antidepressants being SSRIs[22]. Tricyclic anti-depressants, commonly prescribed drugs followed by SSRIs also account for most adverse reactions[23]. In this study, no new findings were observed. The incidence of insomnia and dry mouth were high (>30%) in the polytherapy cohort while in the monotherapy cohort, constipation and dry mouth were the most commonly reported AEs (>30%). The overall frequency of AEs was comparable between the cohorts. Although it is known that combination of Amitriptyline with Mirtazapine alters the pharmacokinetics of the either to a minor extent[24], no specific finding was reported in this study.

This study had few limitations. As the sample size for the study was limited, separate comparisons of polytherapy *versus* monotherapy in each study drug cohort could not be made. Additionally, the adjuvant drugs belonged to multiple categories, hence, definite conclusions on which adjuvant therapy was most appropriate could not be deduced.

## Conclusion

Overall, our findings are consistent with previous literature that support the use of add-on polytherapy for depression[13]. The reason for significantly better results achieved by polytherapy could be simultaneous activation of multiple pathways combined with reduced AEs by dose reduction of the key anti-depressant. This study demonstrated superior efficacy of polytherapy over antidepressant monotherapy in reducing HAM-D 17 scores and improving suicidal ideation/behavior in patients with MDD in India. The safety profile of both the cohorts was comparable.

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**Conflict of Interest :** None

**Data Availability Statement :** The datasets for this study are not available publicly. However, they can be shared by the corresponding author based on specific requests by qualified researchers.

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Original Article

# A Study on Association Between Serum Uric Acid and Non-alcoholic Fatty Liver Disease

**Varun A[1], Kirubhakaran K[2], Pravin Selvam S[3], Ranga Bashyam S R[2]**

**Abstract**

**Background :** Non-alcoholic Fatty Liver Disease (NAFLD) is a prevalent liver condition linked with metabolic syndrome, characterized by fat accumulation in the liver without significant alcohol intake. Elevated Serum Uric Acid (SUA) levels are proposed as a potential marker for metabolic disorders, including NAFLD.

**Materials and Methods :** This cross-sectional study aims to investigate the association between SUA levels and NAFLD in a cohort of 1021 patients from a single center in India. Patients were assessed for demographic, clinical, and biochemical parameters. NAFLD was diagnosed using hepatic ultrasound.

**Results :** The study found a 32.9% prevalence of NAFLD among 336 patients. Mean SUA levels were significantly higher in the NAFLD group (6.5 ± 1.9 mg/dL) than in the non-NAFLD group (5.6 ± 1.7 mg/dL, $p < 0.001$). Each 1 mg/dL increase in SUA was linked to a 25% higher odds of NAFLD (OR 1.25, 95% CI 1.18 - 1.33, $p < 0.001$). Other significant predictors included age (OR 1.02 per year, $p < 0.001$), male gender (OR 1.35, $p = 0.008$), BMI (OR 1.10 per kg/m², $p < 0.001$), hypertension (OR 1.45, $p < 0.001$), and diabetes mellitus (OR 1.30, $p = 0.021$).

**Conclusion :** Elevated Serum Uric Acid (SUA) levels are significantly associated with non-alcoholic fatty liver disease (NAFLD), with a 25% increase in odds for each 1 mg/dL rise in SUA. SUA could be a useful biomarker for early NAFLD detection, aiding preventive and therapeutic strategies.

**Key words :** Non-alcoholic Fatty Liver Disease, Serum Uric Acid, Metabolic Syndrome, Obesity.

Non-alcoholic Fatty Liver Disease (NAFLD) encompasses a range of liver conditions from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, strongly associated with metabolic syndrome, obesity, type 2 diabetes, and dyslipidemia[1,2]. NAFLD poses significant public health challenges due to its potential progression to severe liver disease and its link to cardiovascular diseases. Insulin resistance is central to NAFLD, leading to hepatic steatosis, while progression to NASH involves oxidative stress and inflammation[3,4]. Diagnosis typically relies on imaging techniques like ultrasound. Elevated Serum Uric Acid (SUA) levels, common in metabolic disorders, are associated with an increased risk of NAFLD through mechanisms such as oxidative stress and inflammation, making SUA a potential biomarker for early identification and management of NAFLD[5,6].

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***Editor's Comment :***

- Elevated Serum Uric Acid (SUA) levels are strongly associated with NAFLD, with each 1 mg/dL increase raising the odds by 25%.
- Monitoring SUA levels could aid in early NAFLD detection, allowing for timely intervention and risk reduction strategies. Integrating SUA assessment into routine metabolic screening may enhance preventive care for NAFLD.

## Prevalence :

NAFLD affects approximately 25-30% of the global population, with higher prevalence rates reported in individuals with obesity and type 2 diabetes. The condition is particularly prevalent in developed countries due to lifestyle factors such as poor diet and sedentary behavior[7].

## Rationale :

Previous studies have suggested a link between SUA levels and the severity of liver disease. Elevated SUA has been associated with various metabolic abnormalities, including insulin resistance, hypertension, and dyslipidemia, which are common in NAFLD[8,9]. However, the relationship between SUA and NAFLD in broader populations remains under-explored. This study aims to explore this relationship

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and assess whether elevated SUA levels can serve as a biomarker for NAFLD.

## Materials and Methods

### Study Design and Population :

This cross-sectional study was conducted at a single center in India and included a total of 1021 patients. Data were collected from medical records, focusing on patients who had available Serum Uric Acid (SUA) measurements and hepatic ultrasound data confirming the presence or absence of Non-alcoholic Fatty Liver Disease (NAFLD). The study population comprised adults aged 18 years and older who met the inclusion criteria and provided informed consent. The detailed collection of demographic, clinical and biochemical parameters allowed for a comprehensive analysis of the association between SUA levels and NAFLD.

### Inclusion and Exclusion Criteria :

The study included adults aged 18 and older with available Serum Uric Acid (SUA) measurements and hepatic ultrasound data confirming or excluding NAFLD, who provided informed consent. Exclusion criteria were significant alcohol consumption (over 20g/day for women, 30g/day for men), other chronic liver diseases, medications affecting liver fat or SUA levels, pregnancy, breastfeeding, malignancy, severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$), acute or chronic inflammatory conditions, bariatric or obesity surgeries, incomplete medical records and those unwilling to consent.

### Diagnosis of NAFLD :

NAFLD was diagnosed based on hepatic ultrasound findings, which detect hepatic steatosis. Patients were classified into NAFLD and non-NAFLD groups.

### Data Collection :

Data were collected on demographic, clinical, and biochemical parameters, including age, gender, BMI, blood pressure, fasting glucose levels, lipid profiles, and SUA levels. Hypertension was defined as blood pressure ≥140/90 mmHg or current use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or use of antidiabetic medication.

### Statistical Analysis :

Descriptive statistics were used to summarize the data. Continuous variables were expressed as mean ± Standard Deviation (SD), and categorical variables as percentages. Comparisons between NAFLD and non-NAFLD groups were made using t-tests for continuous variables and chi-square tests for categorical variables. Logistic regression analysis was used to evaluate the association between SUA levels and NAFLD, adjusting for potential confounders such as age, gender, BMI, hypertension, and diabetes mellitus. Statistical significance was set at $p < 0.05$.

## Results

### Baseline Characteristics of the Study Population :

A total of 1021 patients were included in the study, with 336 patients diagnosed with NAFLD and 685 patients without NAFLD. The baseline characteristics of the study population are summarized in Table 1.

The NAFLD group had significantly higher mean age, BMI and SUA levels compared to the non-NAFLD group.

### Distribution of Serum Uric Acid Levels :

Fig 1 shows the distribution of serum uric acid levels in NAFLD and non-NAFLD patients. The median SUA levels were significantly higher in the NAFLD group compared to the non-NAFLD group.

### Association between SUA Levels and NAFLD :

Logistic regression analysis was conducted to determine the association between SUA levels and NAFLD, adjusting for potential confounders such as age, gender, BMI, hypertension and diabetes mellitus. Table 2 shows the Logistic Regression Analysis for Association between SUA and NAFLD.

Table 1 — *Baseline Characteristics of the Study Population (n=1021)*

| Characteristic | Total (n=1021) | NAFLD (n=336) | Non-NAFLD (n=685) | p-value |
|---|---|---|---|---|
| Age (years) | 45.8 ± 12.3 | 48.2 ± 11.5 | 44.4 ± 12.6 | <0.001 |
| Gender (M/F) | 580/441 | 210/126 | 370/315 | 0.032 |
| BMI (kg/$m^2$) | 27.5 ± 4.8 | 29.1 ± 5.1 | 26.7 ± 4.5 | <0.001 |
| SUA (mg/dL) | 5.9 ± 1.8 | 6.5 ± 1.9 | 5.6 ± 1.7 | <0.001 |
| Hypertension (%) | 35.2 | 47.6 | 28.2 | <0.001 |
| Diabetes Mellitus (%) | 24.1 | 31.8 | 19.7 | <0.001 |

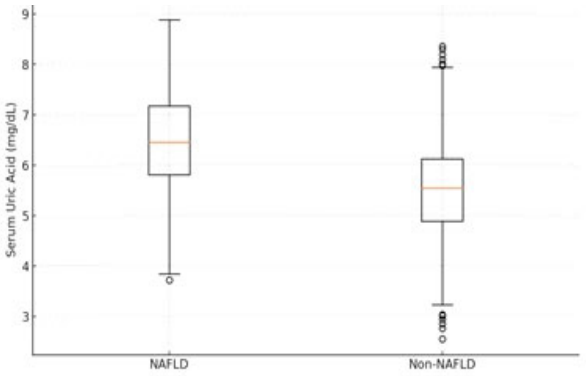


Fig 1 — Distribution of Serum Uric Acid Levels in NAFLD *versus* Non-NAFLD Patients

Table 2 — *Logistic Regression showing Association between SUA and NAFLD*

| Variable | Odds Ratio (OR) | 95% Confidence Interval (CI) | p-value |
|---|---|---|---|
| SUA (per mg/dL) | 1.25 | 1.18 - 1.33 | <0.001 |
| Age (per year) | 1.02 | 1.01 - 1.03 | <0.001 |
| Gender (Male) | 1.35 | 1.08 - 1.68 | 0.008 |
| BMI (per kg/m²) | 1.10 | 1.07 - 1.13 | <0.001 |
| Hypertension | 1.45 | 1.20 - 1.75 | <0.001 |
| Diabetes Mellitus | 1.30 | 1.04 - 1.62 | 0.021 |

### Correlation between SUA Levels and BMI :

Fig 2 illustrates the scatter plot of Serum Uric Acid levels and BMI in NAFLD *versus* non-NAFLD patients. There is a positive correlation between SUA levels and BMI in both groups, with higher SUA levels observed in the NAFLD group.

## Discussion

This study demonstrates a significant association between elevated serum uric acid (SUA) levels and the presence of Non-alcoholic Fatty Liver Disease (NAFLD). SUA remained an independent risk factor for NAFLD after adjusting for potential confounders such as age, gender, Body Mass Index (BMI), hypertension, and diabetes mellitus. The positive correlation between SUA and BMI underscores the critical role of metabolic factors in the pathogenesis of NAFLD. Our findings align with previous research suggesting that metabolic syndrome components are intricately linked with NAFLD, reinforcing the idea that elevated SUA levels are not merely coincidental but may actively contribute to disease pathology[10,11].

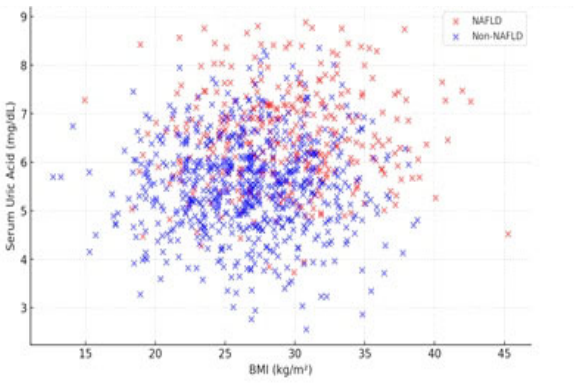


Fig 2 — Scatter Plot of Serum Uric Acid Levels and BMI in NAFLD *versus* Non-NAFLD Patients

The elevated SUA levels observed in NAFLD patients suggest that hyperuricemia may contribute to the development and progression of NAFLD[6,7]. This association is likely mediated by multiple mechanisms, including oxidative stress, inflammation, and endothelial dysfunction, which are known to be influenced by elevated uric acid levels. Hyperuricemia can induce oxidative stress by generating reactive oxygen species, leading to lipid peroxidation and cellular damage in the liver. Additionally, elevated SUA can stimulate the production of pro-inflammatory cytokines, exacerbating hepatic inflammation and promoting the progression from simple steatosis to NASH and fibrosis. Endothelial dysfunction, another consequence of hyperuricemia, can impair hepatic microcirculation, further contributing to liver damage[12,13]. These findings support the hypothesis that SUA is not merely a bystander but an active participant in the pathogenesis of metabolic liver diseases. The interplay between elevated SUA levels and metabolic syndrome components highlights the systemic nature of NAFLD and underscores the importance of a holistic approach to managing this condition[13].

The routine measurement of SUA could be a valuable tool in identifying patients at risk for NAFLD, enabling early intervention and management. Elevated SUA levels, as a potential biomarker for NAFLD, could guide clinicians in stratifying risk and implementing targeted strategies for prevention and treatment. Lifestyle modifications, such as weight loss, dietary changes, and increased physical activity, are cornerstone interventions that can reduce SUA levels and improve metabolic health. Pharmacological treatments aimed at lowering SUA levels, such as xanthine oxidase inhibitors (eg, allopurinol and febuxostat), might also play a role in mitigating NAFLD

progression. However, the long-term benefits and safety of these interventions in the context of NAFLD require further investigation[14-16].

Moreover, incorporating SUA measurement into routine clinical practice could help identify patients who might benefit from more aggressive lifestyle or pharmacological interventions, potentially reducing the burden of NAFLD and its complications. While our study provides valuable insights into the association between SUA and NAFLD, further longitudinal studies are needed to establish causality and determine the effectiveness of interventions aimed at reducing SUA levels in preventing or treating NAFLD. Additionally, research exploring the molecular mechanisms underlying the relationship between SUA and NAFLD could uncover novel therapeutic targets, offering new avenues for managing this increasingly prevalent condition.

The prevalence of NAFLD in our study population was 32.9%, which is consistent with global prevalence estimates. This underscores the high burden of NAFLD in clinical practice and the need for effective screening and management strategies.

### Strengths and Limitations :

One of the key strengths of this study is the large sample size, which provides sufficient power to detect significant associations and allows for generalizability of the findings. Additionally, the comprehensive data collection on various metabolic parameters enables a robust adjustment for confounders in the logistic regression analysis. The use of ultrasound for diagnosing NAFLD adds to the reliability of the diagnosis.

This study has several limitations. First, the cross-sectional design limits causal inference between elevated SUA levels and NAFLD; longitudinal studies are needed for temporal relationships. Second, the single-center setting may limit generalizability. Third, NAFLD diagnosis was based on ultrasound, which, though reliable, is less accurate than liver biopsy. Additionally, potential confounders like dietary habits and genetic predispositions were not considered.

## Conclusion

In conclusion, this study found a significant association between elevated Serum Uric Acid levels and the presence of Non-alcoholic Fatty Liver Disease. Elevated SUA levels were independently associated with NAFLD after adjusting for age, gender, BMI, hypertension and diabetes mellitus. These findings suggest that SUA could serve as a useful biomarker for early identification of patients at risk for NAFLD. Given the high prevalence of NAFLD and its association with metabolic disorders, routine measurement of SUA in clinical practice could aid in the early detection and management of NAFLD. Further research, particularly longitudinal studies, is needed to confirm these findings and to explore the underlying mechanisms linking SUA and NAFLD. The strengths of this study include its large sample size and comprehensive data collection, while limitations include its cross-sectional design and single-center setting.

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Original Article

# A Cross Sectional Study of Fetal Heart Parameters in Gestational Diabetes Mellitus

**Charishma Halemani[1], Santosh S Basarakod[2], Suvarna Guled[3], Chaitra N[4]**

**Abstract**

**Background :** GDM is associated with increased feto-maternal morbidity and mortality. It is estimated that 1 in 4 births are affected by GDM. Constant exposure to high levels of maternal glucose in the intrauterine period, leads hyperglycemia and hyperinsulinemia in the fetus, resulting in altered organogenesis and growth. A condition known as fetal hypertrophic cardiomyopathy, is common in theses fetuses and is characterized by asymmetric myocardial hypertrophy affecting the interventricular septum. This change does not pose a risk to the fetus unless associated with functional impairment. Thus, it is important to monitor pregnant diabetic women for fetal cardiac dysfunction. Echocardiography is a non-invasive, widely available, accurate screening tool for evaluation of fetal cardiac structure and function. Hence, this study was undertaken to contribute in recognizing the importance of fetal heart surveillance parameters in GDM.

**Materials and Methods :** This is a prospective observational study conducted on 150 pregnant women at a tertiary centre in Western Maharashtra from January, 2019 to December, 2021. Women with singleton, uncomplicated pregnancy with Gestational Diabetes Mellitus were included. Fetal echocardiography was done between 24 -28 weeks of gestation and ventricular wall thickness, interventricular septum thickness, ejection fraction, E/A ratio, systolic and diastolic functions were assessed and analyzed.

**Results :** The Mean age of the women with GDM was 27.63 years and mean period of gestation was 25.57 weeks. The mean RV wall thickness, LV wall thickness and IVS thickness was 3.2 mm, 3.5 mm and 3.7 mm respectively. Mean LVEF% was 69.08%, TV E/A ratio 0.7 and MV E/A ratio was 0.8. Normal LV diastolic function was seen in 14.6% cases, while mild, moderate and severe LV diastolic dysfunction was seen in 52.6%, 32% and 0.8% cases respectively. Normal RV diastolic function was seen in 26.6% cases, while mild, moderate and severe RV diastolic dysfunction was seen in 34.6%, 38% and 0.8% cases respectively. Neonatal echo was indicated in 49.3% cases while congenital anomalies were present in 9.3% cases.

**Conclusion :** The present study found an increased interventricular septum among the foetus of mothers with gestational diabetes with no significant cardiac dysfunction.

**Key words :** Gestational Diabetes Mellitus, Fetal Echocardiography, Cardiac Dysfunction.

Globally, the prevalence of diabetes is increasing at an alarming rate. The number is expected to rise from 536.6 million to 783.2 million by 2045[1]. The shift in the work – life balance, sedentary lifestyle, food habits and reduced physical activity has increased the burden of obesity and diabetes in reproductive age group, thus increasing the occurrence of hyperglycemia in pregnancy. The overall prevalence of GDM is between 4-16.5% worldwide[2].

Gestational Diabetes Mellitus (GDM) is any degree of glucose intolerance during the pregnancy and is characterized by onset or first detection in the present pregnancy[3]. Thus, new onset diabetes in pregnancy

***Editor's Comment :***

- Fetal hypertrophic cardiomyopathy is common in pregnancy with gestational diabetes. Though the condition is asymptomatic with no significant cardiac dysfunction, it is important to monitor the fetus in gestational diabetes mellitus. Echocardiography is a reliable, safe, non invasive method for the monitoring of the fetus.

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as well as unrecognized pre-gestational diabetes are included in the definition. Women with GDM develop short term pregnancy complications like pre-eclampsia, cesarean delivery, macrosomia, still birth, shoulder dystocia. In future, there is increased risk of developing type 2 diabetes, cardiovascular problems. About half of the women with history of GDM develop type 2 diabetes in 10 to 20 years after delivery[4]. GDM also has genetic implications, meaning that offspring are at higher risk of obesity, diabetes, hypertension and metabolic syndrome. It is estimated that one in four births are affected by gestational diabetes[5].

In India, the prevalence of GDM varies from region to region, mainly attributed to cultural difference, food habits, socio-economic status and demographic factors. The prevalence in rural areas of central[6] and western[7] India is 1.9% and 12.7% respectively, which is much higher in urban areas, higher socioeconomic status and older age groups[8].There is also variation in the incidence of GDM, depending on the criteria used for the diagnosis, accordingly it is 22.64% with IADPSG criteria, 17.61% with modified Carpenter and Coustan and 13.21% with DIPSI[9].

Constant exposure to high levels of maternal glucose in the intrauterine period, leads hyperglycemia and hyperinsulinemia in the fetus. As the intrauterine growth of fetus is dependent on insulin- Like Growth Factors (IGF-1), increased insulin and endogenous catecholeamines levels exert an anabolic effect, resulting in altered organogenesis and growth[10]. Hyperglycemia has teratogenic effect on heart and leads to myocardial remodeling which may manifest as cardiomyopathy, microvascular protrusions and subcellular issues[11]. A condition known as fetal hypertrophic cardiomyopathy, is common in theses fetuses and is characterized by asymmetric myocardial hypertrophy affecting the interventricular septum. It is believed to be the result of fetal hyperinsulinemia and increased insulin receptors expression and affinity which leads to the proliferation and hypertrophy of cardiac myocytes[12]. These changes do not pose a risk to the fetus unless they are related to functional impairment. Therefore, it is important to monitor pregnant diabetic women for fetal cardiac dysfunction[13].

In recent years, fetal echocardiography has gained popularity and is widely used to evaluate fetal cardiac anomalies[14]. It is a simple, effective and non-invasive technique. Addition of doppler studies, has given an insight into the better understanding of the fetal cardiac function. Diastolic dysfunction is the earliest change of fetal hypertrophic cardiomyopathy with GDM, which can be detected by the fetal echocardiography[15]. The non-invasive nature and wide availability of fetal echocardiography makes it a good screening tool in the low resource country for the evaluation of cardiac function and detection of structural congenital cardiac defects. Hence, the study was undertaken at our tertiary care centre to contribute in recognizing the importance of fetal heart surveillance parameters in gestational diabetes mellitus.

## Materials and Methods

This prospective observational study included 150 pregnant women in a Tertiary Care Centre in Western Maharashtra from January, 2019 to December, 2021. Pregnant women with singleton, uncomplicated pregnancy with gestational diabetes mellitus were included in the study. Pregnant women with pre-gestational diabetes, multiple pregnancy, fetal structural or chromosomal abnormalities and those with medical and obstetric co- morbidities were excluded from the study.

After obtaining an informed consent, medical history and physical examination was done as per a piloted proforma. Maternal information such as age, height, weight, body mass index, gravidity, parity, gestational age and diabetes treatment were noted. The fetal echocardiography was performed by experienced personnel according to American Society of Echocardiography guidelines between 24 to 28 weeks of gestation. Using the Epiq 7 Bothell Ultrasound system for the fetal echo-cardiography, the thickness of the fetal ventricular walls and interventricular septum was measured. Repeat scan after 4 weeks was performed in cases with a suboptimal echocardiographic window or a suspicion of a lesion. Ventricular wall thickness, interventricular septum thickness, ejection fraction, E/A ratio were noted. Both the systolic and diastolic functions were assessed and the parameters were noted. All the neonates with a suspicion or abnormal echocardiographic features were subjected to echo-cardiography at birth.

The sample size was calculated taking into consideration various fetal echocardiographic characteristics with $\alpha$ error of 5%-10% and confidence interval of 95%, the required sample size is shown in

Table 1 — *Sample size estimation*

| Fetal echocardiography characteristics | Mean | SD | α error | Required sample size |
|---|---|---|---|---|
| IVS thickness (mm) | 3.2 | 0.1 | 5% | 15 |
| RV wall thickness (mm) | 3.29 | 0.59 | 10% | 134 |
| LV wall thickness (mm) | 3.41 | 0.57 | 10% | 125 |
| RV EF (%) | 0.26 | 0.16 | 5% | 39 |
| LV EF (%) | 0.25 | 0.12 | 5% | 22 |
| Tricuspid E/A | 0.66 | 0.18 | 5% | 50 |
| Mitral E/A | 0.72 | 0.12 | 5% | 22 |

Table 1. Thus, 150 subjects were included in the present study.

The quantitative data is presented as mean and Standard Deviation and the qualitative data is presented as frequency and percentage. Appropriate statistical software, including but not restricted to MS Excel, SPSS version 20 were used for statistical analysis.

## Results

The mean age of the women in the present study was 27.63 years and the mean period of gestation at the time of foetal echocardiography was 25.57 weeks. Majority were primigravida (44.7%), followed by G2 (34.7%) and G3 (12.7%). 50% (75) of the women were graduate. Among the mothers, there were 11(7.3%) who had past history of gestational diabetes and 32(21.3%) had family history of diabetes.

As shown in Table 2, the mean FBS was 100.59±17.549. The majority of the mothers had HbA1c within 6.5 and there were 7(4.6%) who had HbA1c more than 6.5. The oral glucose tolerance test showed 18(12%) levels less than 92mg/dl at 1 hour and 126 (84%) had ≤180mg/dl at 2 hours and 127(84.7%) had ≤153mg/dl levels at 3 hours. 22.7% (34) women were managed on MNT, while 44.4%(65) were on MNT + OHAs. 10%(15) women required insulin and 16%(24) required both OHAs and insulin.

Table 2 — *Baseline maternal characteristics*

| Parameters (n=150) | Minimum | Maximum | Mean | SD |
|---|---|---|---|---|
| Age (in years) | 19 | 38 | 27.63 | 4.107 |
| Period of gestation (in weeks) | 23 | 35 | 25.57 | 1.891 |
| Weight (in kg) | 41 | 95 | 66.03 | 10231 |
| Height (in cm) | 127 | 165 | 155.8 | 4.421 |
| BMI | 17 | 43.47 | 27.23 | 4.28 |
| Blood glucose values : | | | | |
| Fasting (mg/dl) | 72 | 202 | 100.59 | 17.549 |
| Post prandial (mg/dl) | 88 | 202 | 132.19 | 21.613 |
| HbAIC (%) | 4 | 7.9 | 5.592484 | 0.645795 |

In our study, the mean Right Ventricular wall thickness was 3.2 mm, mean Left Ventricular wall thickness was 3.5 mm and the mean Inter Ventricular Septal thickness was 3.7 mm. The detailed structural parameters are shown in Table 3.

The normal blood flow into the ventricles consists of a biphasic waveform in which the initial flow coincides with the E- wave which is the passive filling period of the ventricle and the late flow coincides with the A-wave. The functional parameters of our study are shown below (Table 4).

Congenital anomalies were present in 9.3% (14) cases. The commonest anomalies seen were the renal anomalies like dilated renal pelvis, pyelectasis

Table 3 — *Structural parameters of fetal echocardiography*

| Parameters (in mm) | Number | Percentage |
|---|---|---|
| **Right ventricular wall :** | | |
| 2.5 to 3 | 34 | 22.7 |
| 3.1 to 3.5 | 92 | 61.3 |
| 3.6 to 4 | 22 | 14.7 |
| >4 | 2 | 1.3 |
| **Left ventricular wall :** | | |
| 2.5 to 3 | 3 | 2 |
| 3.1 to 3.5 | 85 | 56.7 |
| 3.6 to 4 | 50 | 33.3 |
| >4 | 12 | 8 |
| **Inter ventricular thickness :** | | |
| 2.5 to 3 | 3 | 2 |
| 3.1 to 3.5 | 41 | 27.3 |
| 3.6 to 4 | 75 | 50 |
| >4 | 31 | 20.7 |

Table 4 — *Functional parameters of fetal echocardiography*

| Parameters (n=150) | Mean | SD |
|---|---|---|
| LV EF % | 69.08 | 2.606 |
| TV – E (m/s) | 36.48 | 6.347 |
| TV -A (m/s) | 47.10 | 7.727 |
| TV – E/A ratio | 0.774 | 0.421 |
| MV – E (m/s) | 39.35 | 6.946 |
| MV – A (m/s) | 48.33 | 7.881 |
| MV – E/A ratio | 0.814 | 0.481 |
| **Parameters** | **Number** | **Percentage** |
| **LV diastolic dysfunction :** | | |
| Normal | 22 | 14.6 |
| Mild | 79 | 52.6 |
| Moderate | 48 | 32 |
| Severe | 1 | 0.8 |
| **RV diastolic dysfunction :** | | |
| Normal | 40 | 26.6 |
| Mild | 52 | 34.6 |
| Moderate | 57 | 38 |
| Severe | 1 | 0.8 |

(LV- Left Ventricle, RV- Right Ventricle, TV- Tricuspid Valve, MV – Mitral Valve, EF – Ejection Fraction, E – E Wave, A – A Wave, SD – Standard Deviation)

of kidneys. Echogenic focus in the LV were the commonest cardiac defects. Two babies also had small mid muscular VSD detected on fetal 2D echocardiography. Choroid plexus cyst was the nervous system anomaly commonly encountered. Neonatal echocardiography at birth was indicated in 49.3% (74) cases due to either suboptimal echocardiographic window or a suspicion of a lesion during fetal echo.

## Discussion

In our study, the mean age of the women was 27.63 years and BMI was 27.23 kg/m$^2$. The mean period of gestation at the time of ultrasonography was 25.57 weeks. In Pooransari P, *et al*[16] study, the mean age was 29.59 ± 5.52 years, mean BMI of 26.36 ± 0.41 kg/m2 and mean gestational age was 23 ± 3.4 weeks (median: 22 weeks). In our study, mean FBS was 100.59 while mean postprandial blood sugar was 132.19, mean HbA1c was 5.59%. The majority of the mothers with GDM was well controlled while 4.6% had poorly controlled GDM.

The effect of maternal hyperglycaemia on the developing fetal heart is complex and multifactorial. During the period of organogenesis, persistent hyperglycaemia leads to increased apoptosis, cell homeostasis, proliferation and migration of neural crest cells, thus affecting the heart and neural tube development[17]. In later gestation, hyperglycaemia attenuates the angiogenic capability of surviving endothelial cells, thus modifying the cardiac function and morphology by controlling total cardiomyocyte number[18]. Hypertrophic cardiomyopathy is a common structural abnormality seen in diabetic mothers, accounting upto 40% of cases[19]. It is characterised by thickening of interventricular septum and free ventricular wall. In our study, according to structural parameters mean RV wall thickness was 3.2 mm, mean LV wall thickness was 3.5 mm while mean IVS thickness was 3.7 mm. In Peng Y-Q, *et al*[20] study, the interventricular septum thickness was 2.76 ± 0.55mm which was significantly thicker in GDM group than the control group. Dervisoglu P, *et al*[13] study also observed that in diabetic group, the fetal Interventricular Septum (IVS) thickness was significantly greater than in non-diabetics ($p<0.05$) but none had an IVS >2 SD from normal. Ghandi Y, *et al*[21] study found using M-mode echocardiography, Interventricular Septum Thickness (IVS) and LV mass were significantly higher in GDM than control group.

A conventional echocardiographic method to measure the diastolic function is to analyse the flow velocities across the Atrioventricular Valve (AV) using pulsed wave doppler which is expressed as E/A ratio. E wave represents the early passive filling velocity caused by ventricular relaxation, while A wave represents the active filling velocity caused by atrial contraction in late diastole[22]. Mitral and tricuspid valve E/A ratio helps to assess the cardiac compliance and preload conditions. It was observed in our study that mean LVEF was 69.08%, mean TV E/A ratio was 0.774 ± 0.421 and mean MV E/A ratio was 0.814 ± 0.481. These findings were comparable to Karaca Kurtulmus S et al study[23] where the TV E/A ratio was 0.7576 ± 0.1282 and MV E/A ratio was 0.7982 ± 0.1140 in GDM group. Similarly, Hou, *et al*[24] study found that mitral valve E/A ratio was 0.637 ± 0.045 and tricuspid valve E/A ratio was 0.702 ± 0.067 in GDM fetus and there was no significant difference seen in mitral or tricuspid valve E/A ratio between the GDM and control groups. Mohsin M, *et al*[25] study observed mitral E/A ratio was lower in gestational diabetes group as compared to the control ($p<0.001$).

In the present study, normal LV diastolic function was seen in 14.6% cases, while mild, moderate and severe LV diastolic dysfunction was seen in 52.6%, 32% and 0.8% cases respectively. Also, normal RV diastolic function was seen in 26.6% cases, while mild, moderate and severe RV diastolic dysfunction was seen in 34.6%, 38% and 0.8% cases respectively. Miranda JO, *et al*[15] showed that diastolic function seemed to be impaired in the right ventricle, with the diabetic group presenting more negative longitudinal early and late diastolic strain rates. Depla AL, *et al*[26] study found a strong association between maternal diabetes and impaired fetal cardiac function in diabetic mothers and concluded that functional changes can occur in the absence of cardiac hypertrophy and also in pregnancies with good glycemic control.

## Conclusion

The present study found an increased interventricular septum among the foetus of mothers with gestational diabetes. The existing nomograms of the fetal cardiac dimensions in the literature are based on the western population. The Indian population do not have the appropriate nomograms. This study will add to the database and may contribute to the research in future

and also aid in preparation of a similar nomogram for the South East Asian population in the upcoming years.

**Ethical Clearance :** The study was approved by the Institutional Ethical Clearance Committee.

**Conflict of Interest :** None declared

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Original Article

# Comprehensive Analysis of Clinical, Laboratory, Radiological Profile and Prognostic Factors in Patients with Scrub Typhus in the South-east Region of Rajasthan:A Single Center Observational Cross-sectional Study

**Divya Airan[1], Shivcharan Jelia[2], Devendra Ajmera[3], Ranjeet Bairwa[4], Yogesh Meena[4]**

**Abstract**

**Background :** To study demographic profile, clinical manifestations, laboratory profile, Radiological profile, and complications in patients diagnosed with scrub typhus admitted to a Tertiary Health Centre in South-east Rajasthan.

**Materials and Methods :** This is an observation cross-sectional study that included 112 patients with Scrub Typhus. After obtaining informed consent, a detailed history was taken and through physical examination was done. All routine investigations such as CBC, Renal Function Tests, Liver Function Tests, Creatine Kinase, ECG, and Chest X-ray were done. If required, higher imaging such as HRCT thorax and 2D-Echo was done. Patients were observed for systemic complications and followed-up till recovery/mortality.

**Results :** 112 patients were enrolled in our study. The mean age of the patients was 44.93 ± 16.84 years with slight female preponderance. Around half of the patients had farming background. 98.2% of patients had fever as the most common presentation followed by myalgia, shortness of breath, nausea and vomiting. On physical examination, Eschar was found in 40 patients. Other findings on physical examination were crepitations, splenomegaly, neck rigidity, and splenomegaly. Around half of total patients had abnormal Chest X-ray. The renal system was most affected organ with involvement in 46.4% of the total patients. Other systems involvement include hepatitis, meningitis, thrombocytopenia, Acute Respiratory Distress Syndrome (ARDS) and myocarditis. Around two-thirds of patients had multiorgan dysfunction. We observed four mortalities in our study (3.6%). Leucocytosis, neutrophilia, raised creatinine, raised creatine kinase, hyperbilirubinemia and raised alkaline phosphatase levels are associated with severity of Scrub Typhus infection.

**Conclusion :** Diagnosis of Scrub Typhus is often missed due to its wide clinical spectrum. Most of the symptoms of scrub are similar to the clinical presentation of other common tropical diseases. Fever with multiple organ dysfunction, acute kidney injury, hepatitis and ARDS should raise suspicion of scrub typhus. Early diagnosis and appropriate treatment can reduce complications associated with scrub and improve outcomes in a positive way.

**Key words :** Scrub Typhus, Multiorgan Dysfunction, Acute Respiratory Distress Syndrome (ARDS).

Scrub Typhus is an arthropod-borne rickettsial disease caused by Orientia tsutsugamushi, an alphaproteobacterium. There are 1 million estimated cases of scrub typhus throughout the Asia-pacific region annually. Bite of the larva (chigger) of trombiculid mites species is responsible for human infection[1]. This is why, the epidemiology of scrub typhus is closely related to epidemiological patterns of trombiculid mites[1]. Habitats of the vector may range from subtropical regions to subarctic regions, semidesert areas, locations with woody vegetation, deep jungles, and rice paddies. Often seasonal variation is seen in scrub typhus with most cases occurring with monsoon and heavy rains[1]. in India, Assam and Bengal witnessed an early epidemic of scrub during the world war but recently many states are affected by the disease including Himachal Pradesh, Jammu and Kashmir, Rajasthan, Tamil Nadu, Kerala, Maharashtra, Bihar, Karnataka and West Bengal[2,3].

***Editor's Comment :***

- Scrub Typhus presents with a wide range of clinical features that often mimic other tropical illnesses, making timely diagnosis challenging. In endemic areas, patients presenting with fever and multiorgan dysfunction – especially renal involvement, hepatitis, or ARDS – should prompt consideration of Scrub Typhus. Early recognition and appropriate management are crucial to reduce complications and mortality.

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Clinical manifestations of scrub are fever, chills, headache, cough, nausea, vomiting, body ache and skin rash. These symptoms are nonspecific and may be confused for viral infections or malaria. Scrub usually involves multiple systems and is associated with systemic complications such as Myocarditis, Pneumonia, Acute Renal Failure, Meningitis, Meningoencephalitis, Gastrointestinal (GI) Bleeding, And Multi-organ Dysfunction Syndrome (MODS)[3]. Therefore Without prompt treatment, the case fatality rate varies up to as high as 30% to 45%[4]. timely diagnosis and early treatment may reduce these complications and improve survival in these patients.

Scrub typhus is associated with various laboratory parameters abnormalities such as thrombocytopenia, hyperbilirubinemia with raised liver enzymes[5,6], renal failure as evidenced by elevated serum creatinine and oliguria[5,6], deranged lipid profile with hyper-triglyceridemia[7].

Treatment of scrub typhus is antimicrobial agents such as Doxycycline and Azithromycin. less preferred antibiotics are Chloramphenicol and Rifampicin. Doxycycline is given in dosing of 100 mg twice a day either orally or intravenous. Azithromycin can be used as an alternative or in case of resistance to Doxycycline[8].

This study is done in patients of Scrub Typhus in South-east Rajasthan with the aims of studying the epidemiological profile, clinical profile, laboratory features, radiological profile and clinical outcomes of this disease.

## Materials and Methods

### Study Design :

This is a Cross sectional Observational study.

### Setting :

This study was conducted in Department of General Medicine, Government Medical College, Kota and Group of associated hospitals, Kota. Study was conducted in the year 2022-23.

### Participants : Inclusion and Exclusion criteria

All the admitted with acute febrile illness cases were potentially eligible for study. Serum IgM ELISA for Scrub Typhus positive patients were final study candidates. Patients less than 12 years were excluded from this study.

### Ethical Approval :

Ethical clearance was taken from Institutional Ethical Committee of Medical College. All the patients were explained in detail about this study and written informed consent was obtained for each patient before their enrollment in the study.

### Methodology :

All the patients of Scrub Typhus after satisfying inclusion and exclusion criteria were investigated for various laboratory parameters such as complete blood count, liver function tests, renal function tests, Creatine Kinase-MB (CK-MB), triglycerides and electrolytes. Detailed history of each patient was taken for demographic data, clinical history and past history. All patients gone through general physical examination and systemic examination. Other investigations such as ECG, Chest X-ray, ABG, NCCT head were done if indicated. Clinical course of all the patients was monitored for respiratory failure, circulatory failure or any other complications. All the patients were followed till the end point like recovery/ death.

### Statistical Analysis :

Data were entered in Microsoft Excel 2017 and analyzed using IBM SPSS statistics version 26. Among the nominal variables, the number and percentage were presented. The data were analyzed by descriptive statistics. Tests such as Chi square test, Mann-Whitney tests were used for statistical analysis.

## Results

Total of 168 patients above the age of 12 years were admitted in our ward and ICU with acute febrile illness. Out of these, 122 patients were found IgM ELISA positive for scrub typhus. 10 patients refused for consent. Finally, 112 patients were included in our study (Fig 1).

### Demographics :

Our study comprised 112 patients with Scrub Typhus, the median age was 44 years with a mean age of 44.93 ± 16.84 years. Females were slightly higher in proportion with 60 females out of 112 (53.6%). Most subjects were housewives 48.2 %, followed by farmers (46.4 %) and others (5.4%). Four patients were hypertensive (3.6%), two were diabetic (1.8%), 2 had history of coronary artery disease (1.8%) and

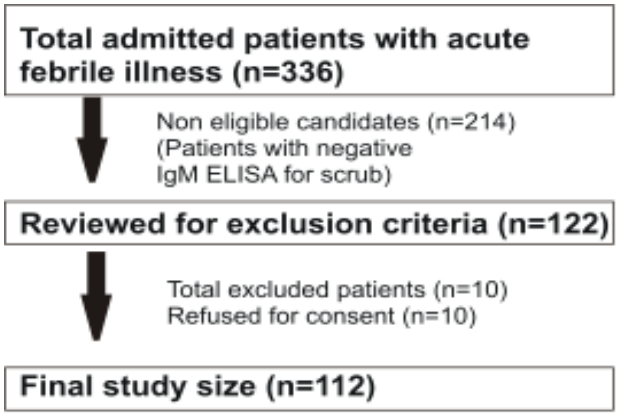


Fig 1 — Study flowchart

2 were known case of chronic kidney disease (1.8%)(Table 1).

## Clinical Profile :

Most common presenting symptom was fever and was present in 100% patients followed by myalgia (55.4%), shortness of breath(44.6%), nausea and vomiting (42.9%), headache (37.5%), pain abdomen (25%), cough (25%), altered sensorium (10.8%), oedema (8.9%), vertigo (3.6%), and seizures (3.6%). An eschar was observed in 40 cases with scrub typhus (35.7%), in this study. During physical examination, 30.7 % patients had crepitations on auscultation, 26.8% had splenomegaly and two patients had lymphadenopathy. two patients (1.8%) with altered sensorium had neck rigidity too.

## Lab parameters :

In our study, the mean hemoglobin was 11.145 gm. Patients in this study had a mild elevation in their total leukocyte counts with a mean of 10176 cells/$mm^3$. Thrombocytopenia was seen in 72.8 % of patients with a mean platelet count of 90285 cells/$mm^3$. 46.4% had derangement in renal function (creatinine more than 1.2) with a mean creatinine of 1.42 mg%. The liver function test showed an elevation of serum bilirubin levels in 39.2% of patients (bilirubin >1.2mg/dl). Mean bilirubin was also elevated with a mean value of 1.9 mg/dl. There was a mild elevation in liver enzymes; both SGOT and SGPT were elevated, with a mean of 148.2 IU/L and 105.5 IU/L respectively. This shows an increase in SGOT was more than the SGPT. Hypertriglyceridemia was seen in our study with mean triglycerides level of 305.33 mg/dl

## Radiological Profile :

In the present study, most patients had pleural effusion on chest imaging (26.8%). Other findings include bilateral pneumonia (21.4%), unilateral pneumonia (3.6%), and Ground-glass opacity (19.6%). 24 patients (21.4%) had Acute Respiratory Distress Syndrome (ARDS). 17.8 % of patients had Hilar lymphadenopathy and mediastinal lymphadenopathy. Cardiomegaly was seen in 3.6% of patients (Table 2).

On USG abdomen examination, 30.3% of patients had splenomegaly followed by hepatomegaly in 26.8% of patients and ascites in 5.4% of patients.

14 patients were taken for 2D-Echocardiogram (2D-Echo), out of which 12 (10.8% of total) patients had myocardial dysfunction.

## Organ System Involvements :

SOFA score was used for the assessment of organ dysfunction and failure. On the basis of SOFA score, organ involvement was classified as organ

Table 1 — *Baseline characteristics of the study population*

| Characteristics | n | Percentage |
|---|---|---|
| **Age :** | | |
| <25 | 18 | 16.1% |
| 26-40 | 32 | 28.6% |
| 41-55 | 26 | 23.2% |
| >55 | 36 | 32.1% |
| **Gender :** | | |
| Male | 52 | 46.4% |
| Female | 60 | 53.6% |
| **Occupation :** | | |
| Farmers | 54 | 48.2 |
| Housewives | 52 | 46.4 |
| Others | 6 | 5.4 |
| **Co-morbidity :** | | |
| Hypertension | 4 | 3.6% |
| Diabetes | 2 | 1.8% |
| Coronary artery disease | 2 | 1.8% |
| Chronic kidney disease | 2 | 1.8% |

Table 2 — *Radiological features observed in Scrub Typhus*

| Radiological Investigations | n | Percentage |
|---|---|---|
| **Chest X-ray and HRCT Thorax :** | | |
| Unilateral pneumonia | 4 | 3.6% |
| Bilateral pneumonia | 24 | 21.4% |
| Pleural effusion | 30 | 26.8% |
| Acute Respiratory Distress Syndrome | 24 | 21.4% |
| Hilar lymphadenopathy | 20 | 17.8% |
| Mediastinal lymphadenopathy | 20 | 17.8% |
| Ground-glass opacity | 22 | 19.6% |
| Cardiomegaly | 4 | 3.6% |
| Ultrasonography (USG) | | |
| Splenomegaly | 30 | 26.8% |
| Hepatomegaly | 34 | 30.3% |
| Ascites | 6 | 5.4% |
| 2D-Echocardiogram | | |
| Myocardial dysfunction | 12 | 10.8% |

dysfunction and organ failure. A SOFA score of 1 or 2 was considered organ dysfunction while a score of 3 or 4 was considered as organ failure. SOFA score was calculated for each patient. Hematological organ involvement was most prominent with 78.6 % followed by renal involvement (46.4%) and hepatic involvement (39.3%). Cardiovascular system and respiratory involvement were seen in 25 % of patients each. The central nervous system involvement was least commonly affected in (10.7%)(Table 3).

In our study, none of the patients had all six-organ involvement, 7.1% had involvement of five organ systems simultaneously and 64.3% of them had 2 or more organ involvement.

### ECG Profile :

All patients had routine ECG examinations. 32.1% of patients had sinus tachycardia and 5.4% had T inversions in ECG. 3 patients had tachyarrhythmias too, comprising of 2 with atrial fibrillation (3.6%) and one with supraventricular tachycardia (1.8%).

### Complications :

About two third of total patients (64.3%) had MODS in the present study. Hepatitis was seen in 33.9% of patients. 23.2% of patients with shock required vasopressor support. Around 21.4% of cases had ARDS requiring ventilation support. Other complications were Meningitis (1.8%), and AKI with creatinine >1.5 mg/dl in 30.4% of the patients. In 12 patients (10.8%), myocarditis was also present (Table 4).

The average duration of hospital stay was 6.64 ± 3.25 with a median duration of 6 days. Around 48.2% of patients required ICU admission. Ventilatory support was required in one-fourth of patients. Among these, 10.7% of cases required non-invasive ventilation, and 14.3% required invasive ventilation. None of the patients in our study required hemodialysis as all patients with acute renal failure were managed conservatively. There were four mortalities in our study.

### Prognostic Factors :

Patients were categorized into three groups based on disease severity, ie, severe (patients with involvement of three or more organs), moderate (patients with involvement of two or fewer organs) and mild (patients without any organ involvement) (Table 5).

There was no statistically significant difference in severity based on gender of patients but it was observed that patients falling in a higher age group had more chances of severe infection(p-value <0.001). Chronic co-morbidities did not have a statistically significant impact on the prognosis of patients. Various laboratory parameters such as total leucocyte counts, platelets, creatinine, creatine kinase, bilirubin and alkaline phosphatase levels had statistically significant co-relation with the severity of scrub infection.

Table 3— *Organ failure assessment based on sequential organ failure assessment score (SOFA score)(n=100)*

| **Organ Involvement – SOFA score of at least 1** | | |
|---|---|---|
| Organ Involvement | n | Percentage |
| **Renal system** : | | |
| Renal Involvement | 52 | 46.4 |
| **Liver** : | | |
| Liver Involvement | 44 | 39.3 |
| **Cardiovascular System (CVS)** | | |
| CVS Involvement | 28 | 25 |
| **Respiratory System** | | |
| Respiratory Involvement | 28 | 25 |
| **Hematological System** | | |
| Hematological System Involvement | 88 | 78.6 |
| **Central Nervous System** | | |
| CNS Involvement | 12 | 10.7 |

| Number of organs involved | N | Cumulative percentage |
|---|---|---|
| **No organ involved** | 10 | 100 |
| One | 30 | 91.1 |
| Two | 30 | 64.3 |
| Three | 28 | 37.5 |
| Four | 6 | 12.5 |
| Five | 8 | 7.1 |
| Six | 0 | 0 |

## Discussion

Scrub typhus is one of the common causes of acute febrile illness during rainy and monsoon seasons in our institute associated with multiple organ

Table 4 — *Complications associated with scrub typhus*

| Outcomes | n | Percentage |
|---|---|---|
| Myocarditis | 12 | 10.8% |
| Meningitis | 2 | 1.8% |
| Acute Respiratory Distress Syndrome | 24 | 21.4% |
| Acute Kidney Injury | 34 | 30.4% |
| Shock | 26 | 23.2% |
| Hepatitis | 38 | 33.9% |
| Multiple Organ Dysfunction Syndrome | 72 | 64.3% |
| Intensive Care Unit (ICU) Requirement | 54 | 48.2% |
| Vasopressors Requirement | 26 | 23.2% |
| Ventilation Requirement | 28 | 25% |
| Non-invasive Ventilation | 12 | 10.7% |
| Invasive Ventilation | 16 | 14.3% |
| Hemodialysis Requirement | 0 | 0% |
| Duration of Hospital Stay (in Days) | 6.64 ± 3.25 | |
| Mortality | 4 | 3.6% |

Table 5 — *Various prognostic factors for Scrub Typhus*

| Parameters | | Severity Groups | | | p-value |
|---|---|---|---|---|---|
| | | Mild (n=10) | Moderate (n=60) | Severe (n=42) | |
| **Gender** | | | | | |
| Male | | 5 | 27 | 20 | 0.9397 |
| Female | | 5 | 33 | 22 | |
| **Age** | | | | | |
| <25 | | 6 | 11 | 1 | <0.001 |
| 26-40 | | 2 | 25 | 5 | |
| 41-55 | | 1 | 15 | 10 | |
| >55 | | 1 | 9 | 26 | |
| **Co-morbidities** | | | | | |
| Present | | 1 | 3 | 6 | 0.2678 |
| Absent | | 9 | 57 | 36 | |
| **Lab Parameter (Mean ± SD)** | | | | | |
| Hemoglobin (Hb) | (gram/dl) | 11.2 ± 2.4 | 11.3 ± 2.4 | 10.9 ± 2.3 | 0.743 |
| Total Leucocyte Count (TLC) | (cells per $mm^3$) | 9745.02 ± 4683.70 | 10149.71 ± 4893.2 | 12623.09 ± 5782.3 | <0.001 |
| Neutrophils | (%) | 67.08 ± 15.02 | 72.7 ± 13.5 | 79.4 ± 12.4 | 0.037 |
| Platelets | (Cells per $mm^3$) | 119523.77 ± 107363 | 97509 ± 82019.37 | 56009.34 ± 54812.81 | <0.001 |
| Creatinine | (mg/dl) | 1.19 ± 0.67 | 1.54 ± 0.65 | 2.9 ± 0.95 | <0.001 |
| Creatine Kinase | (mg%) | 179.40 ± 239.8 | 231.57 ± 312.43 | 438.77 ± 612.4 | <0.001 |
| Bilirubin | (mg/dl) | 1.47 ± 1.59 | 3.47 ± 4.12 | 5.24 ± 6.92 | <0.001 |
| SGOT | (IU/L) | 125.2 ± 156.2 | 213.6 ± 189.4 | 197.57 ± 210.8 | 0.576 |
| SGPT | (IU/L) | 115.4 ± 139.7 | 183.7 ± 181.8 | 167.25 ± 249.1 | 0.602 |
| Alkaline Phosphatase | (IU/L) | 127.6 ± 174.9 | 162.1 ± 199.3 | 201.9 ± 246.3 | <0.001 |
| Triglycerides | (mg/dl) | 325.91 ± 276.1 | 341.76 ± 299.1 | 301.3 ± 247.9 | 0.823 |
| **Duration of hospital stay in days (Mean ± SD)** | | | | | |
| Days | | 5.34 ± 2.9 | 5.98 ± 3.4 | 7.44 ± 4.21 | 0.012 |

dysfunction. In our study, most of the patients were in the age group of 26 to 40 years (28.6%) with a slight female preponderance (53.6%). Around one-half of the patients were farmers by occupation. This can be explained as in this region, farming is carried by young adults with an increasing number of women working in the fields.

The mean age of patients was 44.93 ± 16.84 years with a median age of 44 years. This is slightly higher than a study done by Chrispal, *et al*[6] in which the mean age of presentation was 45.4 years. Male: Female ratio in our study was 26:30. This female predominance is similar to other studies by Varghese GM, *et al*[9] and Kim DM, *et al*[3]. There was a higher female proportion in study by Griffith M, *et al*[10] too. Around 48.2 % of total patients were farmers and 46.4% were housewives. This trend is slightly in contrast with study by Chrispal, *et al*[6] in which farmers comprised of 38.8% of total patients and 42.9 % were housewives.

In present study, fever was the most common presentation (100%) along with myalgia (55.4%) and breathlessness (44.6%). Other clinical manifestations were nausea and vomiting (42.9%) followed by headache (37.5 %), pain abdomen (25%) and cough (25%). Less common presentations were generalized body swelling (8.9%), vertigo (3.6%) and seizures (3.6%). Twelve patients were in altered sensorium at the time of admission (10.8%).

On clinical examination, Eschar mark on the skin was present in around one-third of patients. Presence of eschar varies widely in different studies ranging from around 37 to 60 percent[6,9,11]. Eschar is a typical feature of Scrub Typhus which indicates the initial site of inoculation by the chigger through which the organism enters the lymphatic system and it can be used as a reliable diagnostic feature. The eschar detection rate may vary according to geographic location and demographics. For example, countries in south-east Asian regions have high eschar detection rates due to differences in skin color helping the identification of eschar marks[12].

Other findings on clinical examination are crepitations (30.7%), splenomegaly (26.8%), and lymphadenopathy (1.8%). One, two patient had neck rigidity.

Scrub Typhus is associated with multiorgan involvement which can lead to an increase in mortality and morbidity if early treatment is not initiated. In the current study, around 64% of patients had involvement of two or more organ dysfunction.

In our study around one-fourth of total patients had respiratory system dysfunction. Respiratory dysfunction is most probably due to pneumonia (25%) and ARDS (21.4%). Charoensak A, *et al*[13] in their study suggested respiratory involvement in 20-72% of patients. Cough and breathlessness, with or without chest infiltrates, are seen in Scrub Typhus which is seen in our study. Respiratory involvement varies in severity from pleural effusion and pneumonitis to severe ARDS warranting mechanical ventilation. Pathogenesis leading to respiratory involvement is the presence of interstitial pneumonia with or without vasculitis[14,15]. Our study showed the presence of ARDS in 21.4% of total patients which is significantly higher compared with previously done studies. Past studies showed an incidence of ARDS ranging from 10 to 15%[16,17]. Around two third of patients had abnormal chest skiagram and HRCT scan of Thorax. Abnormality in chest radiography was reported in 59–72% of cases based on studies done by Charoensak A, *et al*[13] and Choi YH, *et al*[18]. In our study, one-fourth of patients required ventilatory support. 10.7% of patients required non-invasive ventilation and 14.3% needed invasive ventilation.

CNS involvement is seen in the form of meningitis, meningoencephalitis, encephalomyelitis or focal neurological deficits. Study by Chrispal A, *et al*[6] suggests that altered sensorium is most common neurological feature of Scrub Typhus present in around 20 to 30% of patients which is higher than the incidence of altered sensorium in our study (10.8%). In our study, 12 patients (10.8%) had CNS involvement based on SOFA score. Only two patient (1.8%) had meningitis in our study. None of the patients had focal neurological deficits in our study.

Hepatic involvement is seen in the form of raised liver enzymes. it is a consistent finding (60-90%) in various studies[5,6]. In the present study, hepatic dysfunction was slightly lower compared with previous studies involving two-thirds of total patients. In our study, there was hyperbilirubinemia in 39.3% of patients with a mean bilirubin level of 1.93 mg/dl. Both SGOT and SGPT were elevated with mean values of 148 IU/L and 105 IU/L respectively. Raised bilirubin levels were associated with severe scrub infection.

Renal involvement was seen in around half of the patients suggested by deranged renal function tests with a mean creatinine value of 1.42 mg/dl. This proportion is a little bit higher than the results from previous studies[9,11,19] suggesting renal involvement in 30 to 40% of patients. However, no patient needed hemodialysis support. We observed that severe scrub infections were associated with raised creatinine values.

Thrombocytopenia is a characteristic laboratory feature of Scrub Typhus and was present in 78.6% of total patients, localized and generalized vasculitis can be considered as a potential cause of thrombocytopenia[9,11]. In the current study, the hematological system was most commonly involved with around four-fifth of patients having thrombocytopenia. However, none of the patients required platelet transfusion. Tsay and Chang, *et al*[17] found decreased platelet counts in severe Scrub Infections. Our study reported a significant association of thrombocytopenia with the severity of Scrub Typhus infection. In our region, Dengue fever also has similar hematological manifestations as scrub typhus along with many similar clinical features. Acute febrile illness presenting with MODS should raise suspicion of scrub typhus.

Previous studies[2,3] have suggested that Scrub Typhus is associated with elevated white blood cell counts and our study also found that raised WBC counts were associated with severe scrub infection. In the current study, it was also observed that neutrophilia is associated with severe Scrub Typhus infection.

In a study by Kalita J, *et al*[21], it was observed that severe scrub infection was associated with raised creatine kinase levels. Our study also had similar results showing higher values of creatine kinase in severe infections.

Based on the SOFA score, 25% of patients had cardiovascular system involvement. Around 23.2% of cases required vasopressor support. The majority of patients requiring vasopressor support were started on Nor-epinephrine and few of them on dobutamine support. Out of 112 patients, most of them (57.1%) had normal ECG. Most common ECG abnormality was sinus tachycardia followed by T inversion (5.4%), atrial fibrillation (3.6%) and supraventricular tachycardia (1.8%). The cardiac profile in Scrub Typhus has not been well studied. In our study, 10.8% of patients had myocarditis which is comparable to a study done by Jung YC, *et al*[20], in which they found myocarditis in 14% of patients.

In our study, 86% of patients had hypertriglyceridemia with a mean triglyceride level of 305 mg/dl. This result is almost similar to study done Sharda M, *et al*[7], which shows raised triglyceride levels in around 92% patients.

The mean and median duration of hospital stay was 6.64 days and 6 days consecutively. Almost half of the patients required ICU support. We observed four mortalities (3.6%) in our study; all 4 of these patients had 5 organ dysfunctions based on SOFA scoring. Both of these patients were intubated for ventilation. Both were having pleural effusion on imaging and two had coronary artery disease as morbidity. Both patient with coronary artery disease were having atrial fibrillation on ECG.

Scrub typhus is a serious infective illness requiring early diagnosis and appropriate treatment. Prompt and timely treatment can reduce life-threatening complications and thus mortality.

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Original Article

# Proportions and Correlates of Postpartum Depression among Mothers from Sunderbans area attending a Tertiary Care Hospital of Eastern India

**Shaily Saran[1], Sumanta Chakraborty[2], Debdutta Haldar[3], Subhrajyoti Naskar[4], Anirban Chatterjee[3], Bibek Paul[5]**

**Abstract**

**Background :** Postpartum depression is a psychological issue which challenges the woman's physical and psychological wellbeing. Prompt screening, early diagnosis and timely management may ameliorate the severity of the condition and may help reduction of maternal and neonatal morbidities.

**Purpose :** In the setting of dearth of published literature for the same in the resource limiting terrains of Sunderbans, this study was done with the objective of exploring the proportions and covariates of postpartum depression among postnatal mothers.

**Materials and Methods :** A cross-sectional hospital based epidemiological study was conducted among 215 postnatal mothers, who were permanent residents of Sunderbans, West Bengal. The study subjects were selected using principles of simple random sampling design. Data on postpartum depression were collected using validated Edinburgh Postpartum Depression Scale (EPDS) and correlates were assessed by a pre-designed pre-tested schedule. Multivariate logistic regression was carried out with all the variables classified under the constructs of factors to determine the affecting factors of post-partum depression after adjusting for confounders.

**Results :** 215 mothers were interviewed, 48 (22.3%) mothers scored ≥13 on EPDS and thus, were categorised as depressed. Illiteracy, early child-birth, giving birth to a female child, lacking of breast feeding of the baby and intimate partner violence were found to be significantly associated with postpartum depression.

**Conclusion :** Proportions of postpartum depression were found to be considerably high. The complex interplay of multiple factors was found to culminate it, upon which socio-economic and lack of psycho-social support system were prominent. A multi-disciplinary approach focusing on timely screening, early diagnosis and appropriate management of the condition and mitigation of the modifiable risk factors can ensure better maternal and child health outcome.

**Key words :** Mental Health, Postpartum Depression, Edinburgh Post-natal Depression Scale, Sunderbans.

Childbirth represents a highly anticipated milestone in a woman's life. However, this remarkable journey into motherhood can be overshadowed by a non-psychotic mental health disorder known as Postpartum depression, which affects an estimated 100 to 150 women per 1,000 births globally[1]. Typically, Postpartum depression manifests after six weeks following childbirth, although it can arise within the first year postpartum[2-4]. This condition is marked by a range of depressive symptoms, including a persistent low mood, feelings of worthlessness, fatigue, loss of interest in activities, diminished appetite and sleep disturbances[3-5]. Research indicates that if Postpartum depression remains undiagnosed and untreated, it can escalate into more severe issues for both the mother and her child. For the mother, there is a significantly increased risk of experiencing recurrent depressive episodes later in

***Editor's Comment :***

- Postpartum Depression (PPD) is a serious mental health condition that affects some women after childbirth. It goes beyond the "baby blues", causing persistent feelings of sadness, anxiety and difficulty bonding with the baby.
- PPD can impact emotional well-being and daily functioning but is treatable with therapy, support and sometimes medication.
- Early identification and seeking help are crucial for recovery, and it's important for new mothers and their support networks to recognize the symptoms and offer assistance.
- Seeking professional help is a sign of strength, not weakness.

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life[6]. For the child, the consequences may include hindered language acquisition and cognitive development. Additionally, the immediate impact of Postpartum depression can impair the mother's ability to engage in essential nurturing activities, such as breastfeeding and caring for the newborn. There is an increasing awareness that the prevalence of Postpartum depression is particularly pronounced in low- and middle-income countries. A systematic review and meta-analysis focusing on postpartum depression in India revealed a pooled prevalence rate of 22% (with a 95% confidence interval of 19-25)[7-8]. Nevertheless, there is a notable lack of research aimed at estimating the prevalence of Postpartum depression among women in various regions of this diverse nation. In particular, the Sunderbans, recognized as a world heritage site, face significant challenges in delivering quality healthcare services to residents living in remote and difficult terrains, often in close proximity to wildlife. The current study aims to assess the prevalence of Postpartum depression and the factors associated with it among women who have recently given birth. By focusing on this specific demographic, the research seeks to fill the existing gap in knowledge regarding postpartum mental health in the Sunderbans region. Understanding the burden of postpartum depression in this context is crucial for developing targeted interventions and improving maternal and child health outcomes. The findings of this study may contribute to a broader understanding of the mental health challenges faced by new mothers in underserved areas, ultimately guiding healthcare policies and practices to better support these women during a critical period of their lives.

## Materials and Methods

This study was a descriptive epidemiological investigation employing a cross-sectional design, conducted at a Tertiary Care Medical College & Hospital that serves a population from the challenging terrains of the Sunderbans, where residents typically exhibit low to moderate socio-economic and educational levels. The research spanned three months, from October, 2022 to December, 2022, focusing on adult women who were mothers of neonates (aged less than one week) and who were proficient in Hindi, Bengali or English, as well as being permanent residents of the area for a minimum of six months. Women who were unwilling or unavailable to participate, as well as those with a prior diagnosis of depression, were excluded from the study.

The sample size was determined using the appropriate formula for cross-sectional studies, aiming for a 95% confidence level and a 5% margin of error, while considering an estimated prevalence of Postpartum depression of 15% among women in Northern India, along with a 10% nonresponse rate[8]. Consequently, the final sample size was established at 215. Participants were recruited in the Postpartum ward and during the immunization and well-baby clinic sessions, which occur bi-weekly at the hospital. Women who fulfilled the inclusion criteria were selected using simple random sampling, with around 5 to 10 women included in each session. Socio-demographic information from the participants was gathered through an interview schedule. The women were evaluated for postpartum depression using the Edinburgh Postnatal Depression Scale (EPDS) devised by Cox[5], *et al*, which is widely regarded as one of the most dependable screening tools for assessing Postpartum depression[9,10]. The EPDS comprises ten items on a Likert scale that evaluate the emotional experiences of women over the past week. In the EPDS, the scoring for questions 1, 2, and 4 follows a 0, 1, 2, 3 sequence from top to bottom, while questions 3 and 5-10 are reverse scored from the bottom up, with each respective score being 3, 2, 1, and 0. A maximum score of 30 is permissible, with a cut-off score of $\geq$10 indicating the presence of Postpartum depression, where higher scores reflect increasing severity of depression[11].

The English version of the scale was linguistically validated into the local language of Bengali. This translation process comprised: (a) a forward translation of the original EPDS into Bengali by a native speaker; (b) a back translation into English executed by another native speaker; (c) the forward and back translation process continued until the back-translated version was consistent with the original English version of the scale; and (d) the translated version underwent pretesting in 30 women who were not part of the study to evaluate its comprehensibility.

The classification of the Socio-economic Status (SES) among the women was based on the revised BG Prasad social classification scale, utilizing the Indian consumer price index for industrial workers for the year 2022. This scale categorizes a person into one of five socio-economic classes, with Class I representing the highest SES and Class V the lowest SES[12,13]. We dichotomized SES into two groups: high/middle SES, which included respondents from Classes I and II, and low SES, which encompassed respondents from Classes III, IV and V.

The participants were evaluated for postpartum depression using the Edinburgh Postnatal Depression Scale (EPDS), which is widely recognized as a reliable tool for assessing postpartum depression. This scale includes ten Likert-scale items that examine women's emotional states over the past week. For items 1, 2, and 4, scores ranges from 0 to 3, while questions 3 and 5-10 use reverse scoring, yields scores of 3, 2, 1, and 0 from bottom to top. The total score can reach a highest value of 30, with a cut-off of >10 indicating postpartum depression, and elevated scores reflecting greater levels of depressive symptoms. Variables were categorized under factors related to postpartum depression.

Data was collected utilizing a pre-structured and pretested form, maintaining strict confidentiality throughout. Data entry was conducted in Excel (Microsoft Inc), while statistical analyses were executed using the IBM Statistical Package for the Social Sciences (SPSS) (Version 20.0, IBM). Both descriptive and analytical statistical methods were applied in the analysis. Categorical data were expressed as percentages, and continuous data were reported as means and standard deviations. The relationship between independent variables and postpartum depression was evaluated through univariate analyses utilizing the Chi-square test, with statistical significance established at $P<0.05$. A multivariate logistic regression analysis was completed to identify factors affecting postpartum depression, adjusting for potential confounders and calculating adjusted odds ratios with 95% confidence intervals, considering intervals that exclude 1 as significant. The goodness of fit for each model was assessed using the Hosmer and Lemeshow test.

The study was conducted after the approvals of the Institutional Ethics Committee Diamond Harbour Government Medical College vide letter number DHGMCH/2022/744 dated 09.06.2022. Informed consent was obtained from all the study participants.

## Analysis and Results

### Descriptive of the Study Subjects :

The study participants' mean age was 22.83 years, with a Standard Deviation of 2.36 years. The majority, 126 (58.6%), were Hindus, 169 (78.6%) were from lower socio-economic groups and 58 (26.9%) were illiterate. The majority of mothers (177, 82.3%) were unemployed and over half of the women (146, 67.9%) were from a lower socio-economic level. The overall proportion of Postpartum depression was 22.3% (95% confidence interval 19.52-26.89%), with a median EPDS score of 6.7 (Q1 = 4; Q3 = 10).

### Factors associated with Post-partum Depression:

#### Univariate analysis

The independent variables that had significant effects on the Postpartum depression of the study subjects were as follows, belonging to lower socio-economic status, having history of intimate partner violence, child requiring neonatal intensive care support and those experienced natural disasters in recent past which is quite frequent in the Sunderbans area (Table 1).

#### Multivariable analysis

Table 2 shows three predictive models for predicting the Postpartum depression that were developed for the present study. Model 1 includes only the social factors, Model 2 includes the social and physical parameters related variable and Model 3 includes the psychological variables in addition to the variables in Model 2.

The final model, Model 3, of the multivariate logistic regression analysis, after resolving for confounders,

Table1 — *Univariate Analysis showing the association of factors with Postpartum depression (N = 215)*

| Variables | Postpartum Depression | | OR (95% CI) |
|---|---|---|---|
| | Absent N;(%) | Present N;(%) | |
| Age | 27.6(±6.3) | 21.3(±4.9) | *1.34(1.02-3.88) |
| **Socio-economic Status** | | | |
| Class I,II,III | 64(29.8) | 5(2.3) | 1.00 (Reference) |
| Class IV, V | 103(47.9) | 43(20) | *2.26(1.17-4.41) |
| **Education** | | | |
| Illiterate | 36(16.7) | 22(10.2) | 1.00 (Reference) |
| Literate | 131(60.9) | 26(12.1) | 0.91(0.56-1.48) |
| **Parity** | | | |
| Primipara | 58(26.9) | 14(6.5) | *2.16(1.31-3.57) |
| Multipara | 109(50.7) | 34(15.8) | 1.00 (Reference) |
| **High-risk Pregnancy** | | | |
| Absent | 156(72.6) | 39(18.1) | 1.00 (Reference) |
| Present | 11(5.1) | 9(4.1) | 1.45(0.89-2.35) |
| **Lactational Status** | | | |
| Breast-feeding | 58(26.9) | 11(5.1) | 1.00 (Reference) |
| Formula-feeding | 109(50.7) | 37(17.3) | *2.510(1.219-3.968) |
| **Gender of Child** | | | |
| Male | 81(37.1) | 28(13.0) | 1.00 (Reference) |
| Female | 65(30.2) | 41(19.7) | *1.926(1.237-5.032) |
| **Intimate Partner Violence** | | | |
| Absent | 101(46.9) | 21(9.8) | 1.00 (Reference) |
| Present | 66(30.6) | 27(12.6) | 1.09(0.67-1.81) |
| **Child Requiring Intensive Neonatal Support** | | | |
| Absent | 158(73.5) | 33(15.3) | 1.00 (Reference) |
| Present | 9(4.1) | 15(6.9) | *2.81(1.71-4.60) |
| **Victim of Natural Disaster** | | | |
| Absent | 14(6.5) | 46(21.4) | 1.00 (Reference) |
| Present | 34(15.8) | 121(56.2) | *5.12(2.92-8.99) |

*dnotes statistical significance

Table 2 — *Multivariate models of predictors of Postpartum depression among study subjects*

| Variables | | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|
| Intercept | | -1.867 | -5.371 | -1.638 |
| Socio-demographic variables | Age | *1.151(1.088-1.217) | *1.172(1.096-1.253) | 1.036(0.907-1.184) |
| | **Socio-economic status** | | | |
| | Class IV, V | 0.793(0.201-3.133) | 1.119(0.251-5.000) | 0.606(0.032-11.327) |
| | Class I,II,III | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| | **Education** | | | |
| | Literate | *0.116(0.029-0.468) | *0.107(0.023-0.509) | 0.595(.029-12.016) |
| | Illiterate | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Physical variables | Parity | | | |
| | Primipara | | 1.007(0.181-5.590) | 3.404(0.220-5.584) |
| | Multipara | | 1.00 (Reference) | 1.00 (Reference) |
| | **High-risk pregnancy** | | | |
| | Absent | | 1.00 (Reference) | 1.00 (Reference) |
| | Present | | 1.025(0.241-4.361) | 2.867(0.280-4.391) |
| | **Lactational Status** | | | |
| | Breast-feeding | | 1.00 (Reference) | 1.00 (Reference) |
| | Formula-feeding | | 1.933(0.843-6.549) | *3.435(1.158-5.662) |
| Physiological variables | **Gender of child** | | | |
| | Male | | | 1.00 (Reference) |
| | Female | | | *3.361(1.412-7.538) |
| | **Intimate partner violence** | | | |
| | Present | | | *1.230(1.040-1.610) |
| | Absent | | | 1.00 (Reference) |
| | **Child requiring intensive neonatal support** | | | |
| | Present | | | 1.658(1.335-3.295) |
| | Absent | | | 1.00 (Reference) |
| | **Victim of natural disaster** | | | |
| | Present | | | 1.895(1.087-4.047) |
| | Absent | | | 1.00 (Reference) |

*dnotes statistical significance

identified the following factors as significantly increasing the probability of Postpartum depression ie, belonging to lower socio-economic status, having history of intimate partner violence, child requiring neonatal intensive care support and those experienced natural disasters in recent past.

The present study utilised Receiver Operating Characteristics Curve (ROC) and Area Under Receiver Operating Characteristics Curve (AUROC) to measure the quality of the classification models. It was seen that inclusion of physical factors improved the model ie, AUROC 0.717 in Model 1 to AUROC 0.823 in Model 2. On addition of psychological factors in Model 3 the AUROC improves further to 0.915 (Fig 1/Table 3).

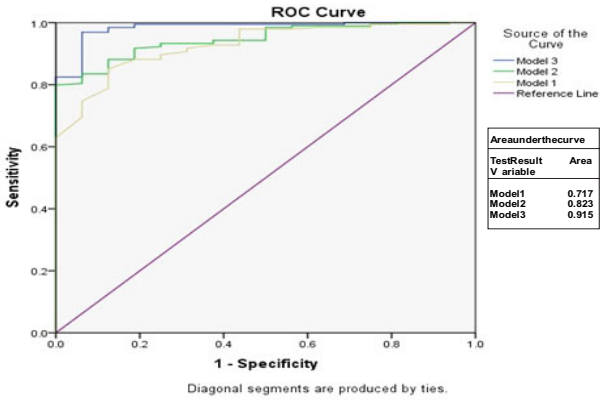


Fig 1 — ROC curve showing the three predictive models

## Discussion

The present study revealed a Prevalence of Post-partum Depression (PPD) at 22.3% among postnatal women, aligning with findings from other studies conducted in India. In rural regions, the reported prevalence of PPD ranges from 12% to 31.4%[14-19], while urban areas exhibit a prevalence between 12.75% and 25.08%[20-22]. Our findings suggest that the prevalence observed in this study is on the higher end of the spectrum reported in various national studies. The discrepancies in prevalence rates may be attributed to differences in research methodologies, socio-cultural factors, levels of poverty, and the challenges associated with basic living conditions in the historically impoverished Sunderbans delta. The widespread illiteracy and lack of awareness regarding mental health issues among mothers in this region, compounded by inadequate healthcare facilities and poor communication

Table 3 — *Model statistics for the three predictive models*

| | Omnibus Tests of Model Coefficient | | | Hosmer | -2 Log | Cox & Snell | Nagelkarke |
|---|---|---|---|---|---|---|---|
| | Chi-square | df | Significance | Lemeshow P | Likelihood | R Square | pseudo R square |
| Model 1 | 44.747 | 3 | 0.000 | 0.975 | 68.387 | 0.192 | 0.461 |
| Model 2 | 50.698 | 6 | 0.000 | 0.852 | 62.435 | 0.214 | 0.515 |
| Model 3 | 82.344 | 11 | 0.000 | 0.714 | 30.789 | 0.324 | 0.779 |

infrastructure, contribute to this situation.

Furthermore, a significant association was found between Postpartum depression and socio-economic status, with higher rates observed among individuals classified as belonging to Classes IV and V. This finding is consistent with numerous other studies that indicate a greater prevalence of depression among lower-income groups[14,20]. The financial constraints imposed by poverty exacerbate mental health issues, particularly when families are faced with the additional responsibilities that come with a new family member.

Having a low birth weight or preterm baby, requiring special support and care was observed to be a predisposing factor for post-partum depression which is similar to another study[20]. There is a significant finding that none of the mothers complained of any psychiatric problems during antenatal period or even before being pregnant. The reasons could be attributed towards the lack of knowledge or some cultural perceptions influencing the reporting of their symptoms.

Psychological factors like intimate partner violence, victims of natural calamities were found to be significantly associated with Postpartum depression in the index studies. Similar, house-hold stressors were reported in other studies both our nation[14-17] and globally[21-26].

Postpartum depression screening by simpler methods like EPDS is highly recommended and should be fundamental to postnatal care in order to avert distressing consequences on mother and child. The women in the postpartum period are likely to have multiple contacts with the health systems, so primary care physician is well placed to identify the warning signs and symptoms of Postpartum depression and could thus provide an adjunct for screening and managing Postpartum depression for the benefit of women, infants and families. Therefore, these providers should be equipped with the correct knowledge and necessary tools for finding optimal solutions to Postpartum depression.

This was a hospital based study, thus selection bias may be an issue which may challenge the external validity of the study. Larger community based studies on the issue are thus warranted. Presence of antenatal depression was beyond the scope of this study due to poor maintenance of medical records by patients in a resource limited settings of Sunderbans. Also, as EPDS is a screening tool for PPD and not a confirmatory one, using multiple validated scales to diagnose presence of probable depression would have increases the internal validity of the study. Nonetheless, the present study reflecting the mental health status of mothers from difficult terrains of Sunderbans will not only give valuable inputs to the extent of this disease entity but shall also apprise the policy makers to assign resources for capacity building in maternal mental health care by evolving and executing new guidelines/ protocols for effective screening, management and the reduction of the burden of Postpartum depression ensuring a safe motherhood for better maternal and child health outcomes.

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## Conclusion

The proportion of Postpartum depression reported in the present study was 22.3%. A complex interplay of social, physical and psychosocial factors play pivotal role in the causation of Postpartum depression. Experiencing natural disasters, being illiterate, belonging to BPL populations, having high-risk pregnancies with neonates requiring intensive support and domestic violence could predict the risk of Postpartum depression. Timely screening, early diagnosis and appropriate management of the condition and mitigation of the modifiable risk factors can prevent emergence of PPD. Most determinants identified by this study can be managed by a continuum of maternal and child health care. Emotional and psychosocial support should be provided by the well knit family and social support

system under the supervision and guidance of community level health care workers to reduce the risk of depression. This study also advocates a monitoring mechanism in which the primary care physicians should screen patients for depression at least once during pregnancy or during the first year post delivery. Additionally, a follow up with behavioural health resources for any patient with a positive screen should also be considered. This will definitely prove to be a cost effective approach in improving Quality of Life for these affected individuals. Hence, the sensitization of the primary healthcare providers and early screening and counselling of the mothers and their families is essential for the reduction of associated morbidities and unfavourable outcomes.

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**Conflicts of Interest :** None

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Review Article

# Twin Deficiency of Calcium and Vitamin D Causes Chronic Pain Syndrome

**Virendra Patil**[1]

**Abstract**

**Background :** Calcium and Vitamin D intake is crucial in bone and calcium metabolism. Low calcium intake is associated with several non-skeletal diseases and non-specific chronic musculoskeletal pain. Calcium is essential for the body, while Vitamin D plays an integral role in calcium homeostasis for maintaining optimum skeletal health. Almost 76% of Indians suffer from Vitamin D deficiency and insufficiency, which also leads to insufficient absorption of calcium, raising calcium deficiency in India.

**Conclusion :** To understand the clinical implications of the twin deficiency of calcium and Vitamin D, the present study aims to review and assess the role of calcium and Vitamin D in chronic non-specific musculoskeletal pains, the role of supplementation in treatment and prevention and offer treatment and prevention recommendations.

**Key words :** Calcium, Vitamin D, Chronic Pain, Musculoskeletal Pain, Calcium Deficiency.

Pain is a common complaint, which may be specific to some body part or diffused. There are several reasons causing pain, including tissue injury, an underlying health condition or an unknown etiology. Chronic non-specific musculoskeletal pain that occurs frequently is a pain that stays for over 3 months and is of idiopathic origin. Chronic pain affects the quality of life, significantly impacting the patient's physical activities, mental health and even social and economic life[1].

Vitamin D deficiency is highly prevalent and is associated with several skeletal symptoms of deficiency. Vitamin D increases the absorption of calcium. Both calcium and Vitamin D is crucial in bone and muscle metabolism[1].

Calcium is an essential nutrient for the body playing an important role in muscle contraction, activation of oocytes, development of strong bones and teeth, blood clotting, nerve impulse, controlling heartbeat, and fluid balance within the cells. Calcium is also important for maintaining general health[2].

Vitamin D plays an integral role in calcium homeostasis for maintaining optimal skeletal health. Calcium is essential for the proper mineralization of bone and strengthens bones. The classic function of Vitamin D is to enhance the efficacy of the intestine in the absorption of calcium and phosphorus. An optimal level of Vitamin D is essential in increasing the efficiency of calcium absorption; its deficiency leads to the absorption of only 10% to 15% of dietary calcium[3]. It is suggested that the combined deficiency of Vitamin D and serum calcium raises the risk of fracture, increases the risk of falling and affects bone mineral density and muscle strength, leading to different pain syndromes. Besides, insufficient dietary calcium and Vitamin D intake can cause a high prevalence of osteoporosis among older persons[4]. Almost 76% of Indians suffer from Vitamin D deficiency and insufficiency in a study including 4624 individuals at 229 sites in 81 cities across the country, the prevalence most common among adults aged 18 to 30 years[5]. This leads to insufficient absorption of calcium associated with Vitamin D deficiency, thereby raising calcium deficiency in India.

The present review aims to study and explore the effect of twin deficiency of calcium and Vitamin D, the role of supplementation in treatment and prevention and provide treatment and prevention recommendations.

***Editor's Comment :***

- The twin deficiency of calcium and Vitamin D is a significant yet often overlooked cause of chronic pain syndrome.
- Ensuring adequate intake of both nutrients is essential for musculoskeletal health, pain management and overall well-being.

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## Materials and Methods

An English-language literature search was conducted using PubMed, Google Scholar and Cochrane database to identify relevant articles. The search terms included 'calcium deficiency,' 'vitamin D deficiency,' 'calcium and Vitamin D deficiency,' 'chronic non-specific musculoskeletal pain,' 'muscle cramps,' 'joint pains,' 'fractures,' and 'calcium and Vitamin D supplementation.' The literature search included case reports, case series, articles, systematic reviews, meta-analyses, and randomized controlled trials. Based on the selected articles, a backward citation search was also performed to search for relevant articles.

### Deficiency of Calcium and Vitamin D :

Calcium and Vitamin D deficiencies lead to abnormal muscular functions such as non-specific pain and weakness. It has been observed in a study that patients with low back pain showed a low calcium intake. Several undetected cases of non-specific muscle pain and weakness are linked to low calcium or Vitamin D intakes. Muscle pain and weakness in many unrelated bone disorders are noted with low levels of Vitamin D in the body[6].

A lack of Vitamin D attributes to skeletal mineralization defect, causing specific or generalized discomfort and aches and pain in joints and muscles. Sometimes, these symptoms also become the reason for misdiagnosing the condition with fibromyalgia, degenerative joint disease, arthritis, chronic fatigue syndrome, or even being dismissed as depression[7].

### Calcium Deficiency :

Calcium deficiency occurs due to inadequate calcium intake, which may cause bone thinning and weakening osteoporosis. If untreated, calcium deficiency can cause serious complications such as osteoporosis, hypertension, and cardiac arrhythmias. Muscle cramping, numbness, and tingling sensation are some of the earliest signs of calcium deficiency. Dry skin and brittle nails also indicate calcium deficiency. Increased menstrual symptoms and bone fractures result from calcium deficiency[2].

Calcium deficiency rarely gets manifested into clinically evident hypocalcemia. Ionized calcium is the main factor causing symptoms in patients with hypocalcemia. Calcium deficiency causes are classified into three major classes: dietary deficiency, calcium malabsorption and Vitamin D-dependent deficiency. There has been growing evidence that sufficient calcium intake is crucial to alleviate deficiency symptoms, achieve optimal peak bone mass and minimize age-dependent bone loss[8].

While low serum calcium levels can affect most organs and symptoms, the common symptom is increased neuromuscular irritability, including perioral numbness, tingling in the hands and feet, and muscle spasms. Postmenopausal women and individuals who avoid dairy products are at an increased risk of calcium deficiency[9].

As we are aware that calcium is important for building bones and maintaining their strength. The weakening of the bones leads to osteoporosis, making the bones porous and fragile. Moderate calcium deficiency causes cramps, joint pains, abnormal growth, muscle cramps, numbness of the arms and/or legs, and brittle nails[2].

### Vitamin D Deficiency :

In the absence of oral calcium intake, calcitriol cannot increase their intestinal absorption. Low dietary calcium and Vitamin D can lead to calcium deficiency, leading to secondary hyperparathyroidism. In the Indian population, twin deficiency of dietary calcium plus Vitamin D is responsible for causing osteomalacia in children and adolescents, while in adults, they lead to osteomalacia[10].

A case series suggested that Vitamin D deficiency and inadequacy play a significant role in chronic pain and muscle spasm in the musculoskeletal system. It has also been observed that treating Vitamin D deficiency and inadequacy may improve symptoms in deficient individuals[11].

Studies have suggested that a low level of Vitamin D is related to the occurrence of both chronic and acute pain. Vitamin D results in anatomic, hormonal, neurological and immunological effects on pain manifestation. Hence, it plays an essential role in the etiology and maintenance of chronic pain stated and associated comorbidities. Vitamin D deficiency also leads to muscle weakness and pain in children and adults[12].

Other studies have indicated that Vitamin D deficiency plays a role in non-specific musculoskeletal pain. It is suggested that mild or early Vitamin D deficiency may lead to skeletal muscle pain, especially in the absence of gross musculoskeletal pathology. Besides, changes in serum calcium levels can also affect

muscle and nerve function. Vitamin D deficiency extended over long durations can also trigger hypocalcemia by disrupting calcium homeostasis. Besides, Vitamin D deficiency also enhances the susceptibility of tissues to inflammation[13].

Various authors have hinted that Vitamin D deficiency could be a reason for initiating non-specific musculoskeletal pain, including low back pain. The nature of the pain associated with Vitamin D deficiency is characteristic, usually sensed in the bone or the muscle[1]. In a study comparing adult OPD patients suffering from non-specific pain in the general body, back, tiredness and weakness were seen to be deficient in Vitamin D[14]. A positive relationship was noted between Vitamin D deficiency and skeletal pain, a link more notable in women than men[15].

## Current and Recommended Supplementation of Calcium and Vitamin D :

### Calcium :

Calcium supplementation is essential for bone health, neuromuscular activity, blood coagulation and optimal cardiac function. It is an integral component of bone architecture and is needed for mineral deposition on bone throughout life. Calcium is absorbed in the small intestines with the help of Vitamin D. The best way to get calcium is through dietary supplements. Those who do not obtain adequate calcium through diet require supplements[16].

### Vitamin D :

Vitamin D is a critical nutrient for maintaining bone health. It regulates calcium absorption and stimulation of bone resorption, thus standardizing serum calcium concentration[16]. Vitamin D supplementation increased 25-hydroxy Vitamin D levels in the serum and therefore has the ability to correct the effects of Vitamin D deficiency[12].

## Calcium and Vitamin D Intake in India :

Adequate calcium intake is necessary to maintain the skeletal mass attained and prevent any ongoing natural loss. India has a prevalence of calcium and Vitamin D deficiency, with the intake of dietary calcium, milk, milk products and cereals reducing drastically over half a century. Surveys have shown that dietary calcium intake (g/CU/day) has undergone a decline from 606 (1975-79) (recommended dietary allowance [RDA]-400) to 433 in the year 2011-2012 (RDA-600). The intake of milk and milk products (g/CU/day) has reduced from 116 (1975-79) to 95 (2011-2012) (RDA-150). While the intake of calcium has been declining in India, the RDA in adult males and females (19-50 years) is 1,000 mg/daily, while in adult males, 51 to 70 years, 1,000 mg and females 51 to 70 years is 1,200 mg[9]. The decline has been observed across different age groups, including infants, children, adults, and pregnant and lactating women[10]. It was seen in a study that the calcium intake in urban India is 308 mg/day, while in rural India, it is 269 mg/day[17].

Calcium and Vitamin D are essential for maintaining bone health, gaining bone mass, and preserving bone with progressing age[10]. Supplementation with Vitamin D and calcium reduces chronic non-specific musculoskeletal pain. It also has the potential to enhance physical activity capacity. Supplementation with Vitamin D and calcium and significant relief in painful conditions also improve the patient's physical, mental and social well-being[1].

In a case study of a patient with non-specific muscle pain that was aggravated if he lifted a heavy bag and progressively worsened, the pain subsided significantly after 3 days of calcium and Vitamin D supplementation. After 2 weeks, the patient was completely relieved of the pain. Non-specific muscular pain and weakness are related to the deficiency of calcium and Vitamin D in the body. The administration of these supplements is known to strongly improve the recovery of a patient with non-specific muscular pain and weakness[6].

Low back pain is a commonly occurring problem. It has been suggested that chronic pain is more prevalent in older women than in men. The back pain in postmenopausal women is attributed to reduce bone mass, sarcopenia, vertebral fractures, and inflammation-deficiencies related to Vitamin D deficiency. Vitamin D supplementation is recommended as therapeutic medication to achieve euvitaminosis D in patients experiencing musculoskeletal pain. In order to manage the pain and weakness caused by Vitamin D deficiency, a holistic approach of appropriate sunlight exposure, Vitamin D plus calcium supplementation and appropriate physical exercise is recommended[18].

Vitamin D should be given in suitable doses to those individuals who are deficient and 'at-risk' populations. It should be accompanied by appropriate age-related calcium administration. Calcium and Vitamin D supplementation in individuals suffering from chronic

non-specific muscular pain may lead to considerable relief in painful conditions. It may also improve physical activity capacity. With the substantial improvement in pain relief, a significant improvement in physical, mental and social well-being also ensues[1].

### Treatment Recommendations :

It has been noted in previous studies that patients with persistent, non-specific musculoskeletal pain were at an enhanced risk of Vitamin D deficiency, which is frequently misdiagnosed[19].

It is recommended that to be effective, calcium and Vitamin D supplementation should be targeted in an individual with documented or at-risk of calcium and Vitamin D insufficiencies. General supplementation in the community is not recommended[20]. Most studies have recommended a combination of minimum doses of 1,200 mg calcium and 800 IU Vitamin D daily[21].

Table 1 provides the Indian Council of Medical Research-National Institute of Nutrition (ICMR-NIN) 2020 recommendations for calcium and Vitamin D in Indians[22].

Calcium carbonate supplements have the highest percentage of calcium amongst available calcium salts. Calcium carbonate has 40% elemental calcium, calcium citrate has 21%, calcium lactate has 13%, and calcium gluconate has 9% elemental calcium. Hence, the number of calcium carbonate tablets needed to maintain optimal daily intake is fewer, thus enhancing patient adherence. A cost-benefit analysis has also revealed that calcium carbonate is one of the less expensive carbonate products. Table 2 provides a comparative account of the different calcium salt supplements[23]. The recommendation is to initiate the calcium/vitamin D supplement at a lower dose and gradually titrate the target intake amount over 1 to 2 months. Calcium carbonate products should be taken with a meal, unlike calcium citrate, which must be taken on an empty stomach or with a flood. Hence, the patient should be properly educated and counselled about using calcium supplementation[16].

Table 2 — *A comparative account of several calcium salt supplements*[23]

| Calcium salts | Calcium (%) | Calcium (mg/g) |
|---|---|---|
| Calcium Carbonate | 40 | 400 |
| Calcium Citrate Malate | 21 | 210 |
| Calcium Acetate | 25 | 253 |
| Calcium Gluconate | 9 | 93 |
| Calcium Phosphate | 38 | 383 |
| Calcium Lactate | 13 | 130 |
| Calcium Orotate | 20.6 | 152.44 |

## Conclusion

Calcium and Vitamin D deficiency is common, and non-specific musculoskeletal pain and lower back pain are common complaints. On the basis of early signs of calcium deficiency, treated should/may be initiated to prevent long-term consequences. Prompt diagnosis and treatment can lead to the resolution of symptoms of chronic musculoskeletal pain and the prevention of osteomalacia, osteoporosis, and other possible long-term complications.

Early signs of calcium deficiency include muscle cramping, numbness, and tingling sensation, while dry skin and brittle nails also indicate calcium deficiency. While Vitamin D deficiency is responsible for low calcium absorption, it also leads to chronic pains, muscle cramping, joint pains, numbness and tingling sensation. Low levels of serum calcium do not lead to a clinical manifestation. Still, moderate calcium deficiency may lead to common symptoms such as neuromuscular irritability, muscle spasms, and tingling in the hands and feet. Calcium requirements in the body are the highest during periods of growth such as childhood, pregnancy, or breastfeeding.

Calcium intake has drastically declined in India over the last half-century. Studies have shown that dietary calcium intake declined from 606 (1975-79) (RDA-400) to 433 in the year 2011-2012 (RDA-600). Calcium supplementation is needed in individuals in whom dietary supplement is insufficient. The recommended daily allowance of calcium in the Indian population is 1,000 mg/day for adult males and females.

Table 1 — *ICMR-NIN 2020 recommendations for calcium and Vitamin D in India*

| Supplement | RDA | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Pregnant women | Lactating women | Infants | Children (1-3 years) | Boys/Girls (10-12 years) | Boys/Girls (13-15 years) | Boys/Girls (16-18 years) |
| Calcium<br>Vitamin D | 1,000 mg/d<br>600 IU/D | 1,000 mg/d<br>600 IU/D | 1,000 mg/d<br>600 IU/D | 1,200 mg/d<br>600 IU/D | 300 mg/d<br>400 IU/d | 500 mg/d<br>600 IU/d | 850 mg/d<br>600 IU/d | 1,000 mg/d<br>600 IU/d | 1,050 mg/d<br>600 IU/d |

Hence, a healthy lifestyle, optimal calcium and Vitamin D, and physical exercise from adolescence are important steps to prevent bone loss, muscle cramps, chronic pains and reducing the risk of fractures. Compliance and adherence are crucial in patients taking calcium and Vitamin D supplements.

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Case Series

# Practice of Covert Administration of Unprescribed Disulfiram in Madhya Pradesh — A Case Series of Disulfiram-induced Psychosis

**Umesh Pathak[1], Amrendra Kumar Singh[2], Rahul Mishra[3], Sneha Shukla[4]**

**Abstract**

**Background :** Disulfiram, an alcohol-aversive agent, is known for its role in alcohol addiction treatment. However, its unsupervised use poses significant risks, including the development of psychosis.

**Case Reports :** This case report presents five patients from different tertiary care centers in Madhya Pradesh, India, who developed psychosis as a result of covert administration of unprescribed disulfiram. After discontinuing disulfiram, the patients were treated with antipsychotic medications, resulting in symptom resolution. This article emphasizes the legal and ethical concerns associated with unauthorized medication administration and highlights the need for public awareness, improved access to addiction treatment, and stricter regulations to prevent the unsupervised use of disulfiram.

**Conclusion :** Healthcare professionals should remain vigilant regarding such adverse effects and closely monitor patients receiving disulfiram.

**Key words :** Disulfiram, Indued Psychosis, Dopamine, Alcohol, Covert Administration.

Disulfiram, an Alcohol-aversive agent, functions by inhibiting the Acetaldehyde Dehydrogenase (ADH) enzyme, thereby leading to the accumulation of acetaldehyde, which elicits unpleasant physiological reactions upon alcohol consumption (Fig 1). Disulfiram has various documented side effects including gastrointestinal disturbances, hepatic complications, dermatological reactions and neurological manifestations[1-4]. Psychosis following Disulfiram administration has been also reported in some cases Worldwide[5-6]. However, limited literature is available on disulfiram-induced psychosis, emphasizing the rarity of this adverse event. While disulfiram-induced psychosis is a rare occurrence, this case series highlights the development of psychosis in individuals who were covertly administered unprescribed disulfiram. We present a case series of five patients from different Tertiary Care Centres in Madhya Pradesh who developed psychosis as a result of the covert administration of disulfiram.

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***Editor's Comment :***

- Disulfiram-induced psychosis, caused by unauthorized self-medication, underscores the risks of unsupervised treatment and the need for professional involvement in addiction care.
- Addressing this issue requires public health campaigns, better access to formal treatment services, and stricter regulations on disulfiram dispensing, along with increased awareness among healthcare professionals to monitor patients closely for adverse effects.

## Case Series

### Case 1 :

A 38-year-old married Hindu male brought to the psychiatric emergency with main complaints of disturbed sleep, suspiciousness and aggressive-violent behavior for two days. He developed a suspicion that someone was trying to harm him and was conspiring against his family. Furthermore, he would accuse others discussing him with malicious intent. These symptoms gradually worsened over the next few days, leading to increased agitation and behavioral disturbances. There was no significant history of any associated medical illness. There was no history of major psychiatric illness in past and family. On substance history, patient was found to be user of alcohol for 3 years but not at dependency level. He was on abstinence for 1-month due restricted accessibility to liquor during COVID lockdown. Patient's general and systemic examination were normal. He was fully conscious and well oriented to time and place. On bed side formal mental status examination findings were anxious and scanning behavior, increased psychomotor activity, difficult rapport establishment, Paranoid and referential delusions, and auditory

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hallucinations. Comprehensive psychiatric evaluation did not revealed any underlying primary psychotic disorder. No sign or symptoms suggestive of alcohol withdrawal and disulfiram-alcohol reactions were noted. His necessary routine investigations were within normal limits. Urine analysis was found negative for recent use of alcohol or other substance metabolites. The findings of EEG, MRI-brain and CSF examinations were within normal limits.

Later, Patient's wife disclosed that she had been secretly administering disulfiram tablets to him for the past 5 days as an attempt to help her husband maintain his alcohol abstinence, fearing that he would not willingly seek treatment. She admitted to obtaining the medication from pharmacy without a prescription. The disulfiram was discontinued immediately. Patient was initially managed with intramuscular haloperidol (5mg) and promethazine (25mg) and then tablet olanzapine 5mg at bedtime was started. Patient's psychotic symptoms started resolving within 2 days of discontinuation of disulfiram and completely vanished in 5-7 days. After the discharge patient was followed up for next 2 months and there was no recurrence of any psychotic symptom. Probable diagnosis disulfiram induced psychosis was made.

### Case 2 :

A 26-year-old unmarried Hindu male, unemployed, came to the Outpatient Department of psychiatry with main complaints of disturbed sleep, hearing of unusual voices and fearfulness for 3-4 days. He began hearing unusual voices that were derogatory and abusive comments towards him. These voices were persistent, occurring throughout the day and caused him significant fear and distress. The patient denied any history of psychiatric symptoms or psychosis in the past and family. There was no significant medical or surgical comorbidity. Patient was user of alcohol for 2 years. He tried to stop alcohol many times and remained in abstinence for more than 2 months but relapsed every time. His last intake was 45 days before. Patient's mother revealed that she was admixing tablet disulfiram 250 mg/day in patient's food for past 5 days without his knowledge which she had bought from chemist without prescription on recommendation from relatives. Patient's consciousness and orientation were intact. No Significant abnormality was detected on clinical examination. Mental status examination findings were anxious affect and auditory hallucinations. He was admitted in the psychiatric ward and comprehensive psychiatric evaluation was conducted, ruling out any underlying primary psychotic disorder. The findings of routine laboratory blood investigations were within normal limits. Urine analysis was found negative for recent use of alcohol or other substance metabolites. EEG, MRI-brain, and CSF examinations were normal.

Disulfiram was stopped and olanzapine 5mg at bedtime was started. Patient recovered over the subsequent 4-5 days. He was discharged and advised to come in follow up in 10 days. In follow up patient's mental state was found normal, olanzapine stopped and his probable diagnosis disulfiram induced psychosis was made. No recurrence of psychosis was noted in next follow ups for 3 months.

### Case 3 :

A 36-year-old married Muslim male, unemployed, referred to the Tertiary Care Center with main complaints of disturbed sleep, self-muttering and suspiciousness for 3 days. He began muttering to himself, often engaging in prolonged conversations without any apparent external stimuli. He also displayed suspiciousness, believing that people were watching him and plotting against him. Family history and past history of psychiatric illness were insignificant. There was no significant medical or surgical comorbidity. Patient had chronic remitting and relapsing history of alcohol use disorder for 12 years. He was on abstinence for 1 month due to religious region during *Ramdaan* period Physical examination, including neurological assessment, was unremarkable. He was conscious and oriented to time, place and person. Mental status examination revealed auditory hallucinations consisting of derogatory voices and persecutory delusion. Laboratory investigations, including complete blood count, electrolytes, liver function tests, and toxicology screen, were within normal limits. CT Brain and EEG showed no significant abnormalities.

Anamnesis obtained from his wife revealed that the patient had given up alcohol 40 days earlier and for 5 days had been on a tablet which they had bought on their own. The tablet was disulfiram 250mg. Wife was mixing a tablet per day in food of patient without awareness of patient. Considering the temporal connection between the consumption of disulfiram and the psychosis onset and ruling out other organic causes, a probable diagnosis of disulfiram-induced psychosis was established. Disulfiram was immediately stopped, and the patient was started on olanzapine 5mg bedtime. Within the following 2-3 days, his psychotic symptoms gradually diminished, leading to resolution. Olanzapine was stopped after 10 days and patient was followed up for 2 months. There was no re-emergence of psychotic symptoms.

### Case 4 :

A 36-year-old male without any past history of neurological and psychiatric illness referred by medical specialist to psychiatry OPD with complaint of self-muttering, unprovoked aggression, suspiciousness against neighbours along with violent behavior for 3 days. There was history of opioid use for 2 years, however his last intake of opioid was 25 days ago due to unavailability of illicit opioid. On examination, there were no sign of withdrawal. On mental status examination, patient was oriented to time, place, person and referential thinking and auditory hallucinations was elicited. All routine investigations and Urinary drug screen were within normal limits. On further enquiry, it was revealed that the patients' wife had initiated medication surreptitiously (Disulfiram

1000mg/day for the last 5 days) for the treatment of substance use on advice of a local pharmacist. Provisional diagnosis of disulfiram induced psychosis was made. Patient was managed with injectable haloperidol for aggression and violent behaviors when required. Patient fully improved over 3 days after stopping disulfiram and subsequently discharged. He has been maintaining well on subsequent 6 months follow ups.

### Case 5 :

A 30-year-old married but separated male, brought by family members with acute-onset fearfulness and self-muttering for 4 days. He had history of Alcohol and opioid dependence for the last 5 years. The patient was maintaining complete abstinence from substances for 3 months as he was kept in a deaddiction facility for 4 months. There was no history of any neuropsychiatric illness. About 3 days prior to the emergence of psychosis, he had started craving for alcohol after attending a social gathering. Hence, family members consulted a local non-registered medical practicener who advised them to mix the tablet into his food and tea. (disulfiram 250 mg thrice daily). 3 days after disulfiram use, patient developed psychotic features. On physical examination, the patient was conscious and well-oriented without any significant neurological deficit. MSE findings were increased psychomotor activity, dysphoric affect, elementary auditory hallucinations and half-formed delusion of persecution. Blood and urine investigations were within normal limits. After admission in psychiatry unit, disulfiram was stopped and patient was with diazepam 5 mg twice daily and 2 mg risperidone for 5 days, which lead to full resolution of psychosis within the hospital stay. Patient was followed up for next 6 months and there was no emergence of psychosis again. Psychotropics were then gradually discontinued.

In all five cases, the treatment plan also included appropriate pharmacological and non-pharmacological management of alcohol use disorder.

## Discussion

Disulfiram is a medication used to support individuals with alcohol addiction by inducing unpleasant effects when alcohol is consumed. However, its availability without a prescription has led to its misuse as a self-administered treatment option for individuals seeking to quit alcohol. In India, Disulfiram, is commonly referred to as “Sharab Chhudane Ki Dawa” (the medicine to wean off alcohol). This case series reported five patients of psychosis induced by the covert use of disulfiram, purchased from a pharmacy without prescription from expert specialist doctor. These patients had a prior history of alcohol abuse. The symptoms in all cases emerged after consumption of disulfiram tablets. Delirium due to disulfiram-ethanol

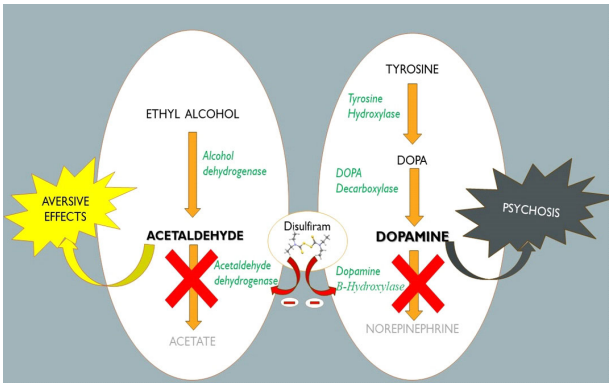


Fig 1 — Mechanism of Disulfiram Producing Aversive Effects and Psychosis

interaction and encephalopathy manifestations induced by disulfiram have been reported in some studies[7,8]. Since patients from our case series had not drunk alcohol while they were being administered disulfiram, the possibility of disulfiram-reaction due to interaction with alcohol was eliminated. Similarly, the patients were in abstinence for at least one month and urine tests did not reveal any findings related to illicit substance. The symptoms of withdrawal usually occur within 6-8 hours after the last drink, reach the peak by 24-72 hours and usually last 1 week. Therefore, the alcohol intoxication or withdrawal would not be the most probable diagnosis. All the patients were fully conscious, attentive and well oriented to time, place and person during presentation and the common laboratory investigations related to delirium were within normal limit. Hence, diagnosis of delirium was not considered. EEG, CT- Brain and CSF analysis findings were normal which ruled out common organic causes of indued psychosis. Lack of past or family psychiatric history, temporal relationship of onset of symptoms with disulfiram consumption and finally, rapid resolution of symptoms after discontinuation of disulfiram were more suggestive of disulfiram induced psychosis rather than a primary psychiatric disorder.

The exact mechanisms underlying disulfiram-induced psychosis are not fully understood. Disulfiram’s influence on neuro-transmitter systems, particularly dopamine, has been proposed as a potential contributing factor. The breakdown product of disulfiram, Diethyldithiocarbamate is an inhibitor of *dopamine-betahydroxylase* (DBH) enzyme which converts dopamine into noradrenalin. Inhibition of DBH enzyme by disulfiram metabolite may cause increase in dopamine levels[9], and may induce psychotic effects. However, further research is necessary to elucidate the precise pathophysiology (Fig 1).

The important issue in these five cases was the over-the-counter sale of non-prescription medications and covert administration by family members without knowledge of patient. The popularity of disulfiram as “*Sharab Chhudane Ki Dawa*” can be attributed to several factors. Firstly, the

societal stigma associated with alcohol addiction often deters individuals from seeking professional help. Lack of awareness about available treatment options and limited access to addiction specialists and rehabilitation centres also contribute to this phenomenon. Furthermore, the relative affordability and easy availability of disulfiram from local pharmacies make it an accessible choice for those attempting to quit alcohol.

This case series raise significant legal and ethical concerns. Family members' actions of obtaining and administering disulfiram without proper authorization or supervision constitute a breach of medical ethics. It is crucial to educate patients and their families about the importance of seeking professional medical advice and avoiding self-medication practices. In cases where a patient lacks capacity to give informed consent, it is essential to follow established legal protocols to ensure the patient's well-being and autonomy are protected.

## Conclusion

Disulfiram-induced psychosis resulting from unauthorized and unsupervised administration of medication highlights the potential risks associated with self-medication and the importance of involving healthcare professionals in treatment decisions. Addressing this issue requires a multi-faceted approach. Public health awareness campaigns must be launched to educate the general population about the risks associated with self-administration of disulfiram. Additionally, improving access to formal addiction treatment services and implementing stricter regulations on the dispensing of disulfiram can discourage its misuse. Collaborative efforts between healthcare professionals, policymakers, and the community are crucial to curbing this practice and providing comprehensive support to individuals struggling with alcohol addiction. It is essential for healthcare professionals also to be aware of such adverse effects and closely monitor patients receiving disulfiram.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported to the journal. The patient understands that their name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflict of Interest :** None

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# Letters to the Editor

*[The Editor is not responsible for the views expressed by the correspondents]*

## Motivating the Medical Journal Editors to Upgrade their Journals — Brief report of JIMA National Assembly of Editors of Medical Journals

Sir, — Apropos to your "Brief report of JIMA National Assembly of Editors of Medical Journals, 3rd edition, published in the JIMA August, 2024 issue. It is the fulfilment of a strong desire to inspire the "Editors" of Medical Journals. True to the spirit of IMA, you have provided the leadership, conceived the idea, contacted the stakeholders, organized the event, arranged for guest experts and took A to Z care of all the participants from various parts of the country, true, a herculean task in a short frame of time!!! All work by you, and your colleagues on JIMA committee. Kudos to you all sir!

The various topics chosen in 15 different scientific sessions and specially –

How to upgrade one's writing skills for Medical Journals

How to Write a Scientific Paper - An Overview

Panel Discussion : Writing An Original Article-Do's and Don'ts

Open Forum Editor's Meet, How to Upgrade Journal

How To Secure Funded Research Projects from Government of India

Many Editors of different medical journals across the country came and exchanged their views as well.

They are stimulating and tail twisting. We are sure, few of them will quickly upgrade their Journal to new standard, transparent, high quality so that Indian medical researchers find a good platform to publish their work and get international visibility.

Then of the tricky issues like- There was an issue of high registration charges & relatively less attendance, can cause some headaches.

There are over 750 medical colleges in our country, and equally talented faculty forming huge author base, struggling to publish their work, in a catch 22 situation, besides NMC mandate, paucity of reviewers, problem of soliciting middle men, many substandard journals, but few countable upgraded Medical Journals to give international visibility to research work[1-5]. It is right time, right forum you have raised the issue and lit the torch, let the light enlighten us!!!

Alas, we had no hint of this event, we were left behind, and missed a fabulous occasion of meeting, participating and contributing in this conference.

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## Correlation of B-type Natriuretic Peptide and HbA1c in Heart Failure

Sir, — Recently I read the article titled "Study of the Prevalence of Type 2 Diabetes Mellitus in Patients with Heart Failure in a Tertiary Care Hospital in Eastern India" published in Volume 121, No.4, April 2023 of Journal of Indian Medical Association. I congratulate the authors for the research work done. Heart Failure (HF) is one of the emerging health problems not only in India but globally as well. The prevalence of Type 2 Diabetes Mellitus (T2DM) is also increasing at an alarming rate. Both these conditions may coexist with T2DM being a risk factor for HF and vice versa. Various studies (Kaiser Permanent, Danish nationwide cohort study, CHARM program, EMPHASIS-HF trial) have been conducted and have found that the incidence of T2DM was higher in HF when followed up over a period of 3 to 5 years. The study has reported prevalence of prediabetes, Diabetes and their association with ejection fraction. It would have been better if information regarding duration and age at onset of heart failure, T2DM in this study was reported.

**Diagnostic test for Heart Failure and Type 2 Diabetes Mellitus :** B-type Natriuretic Peptide (BNP) levels are increased in heart failure. Glycated hemoglobin or $HbA_1c$ levels indicates the glycemic control and is one of the diagnostic criteria for diagnosis of Diabetes Mellitus according to the American Diabetes Association guidelines. HbA1c may be a predictor of mortality in both T2DM and HF as per GISSI-HF study. It has also been shown that glycemic control affects BNP levels. Increased BNP levels may be caused due to poor glycemic control. The exact mechanism of relationship between hyperglycemia and BNP is not understood. It has been postulated that plasma glucose may induce cardiac myocytes which in turn leads to secretion of BNP. Hence, in HF patients with increased BNP levels, plasma glucose and $HbA_1c$ should be evaluated[3]. However, in a multiple regression analysis study, the authors Inoue Y, *et al* have found no correlation between $HbA_1c$ and HF. They also did a multivariate analysis which showed that BNP levels improve insulin resistance and in fact decrease the progression of DM. Since obesity is implicated in development of insulin resistance, relation of Body Mass Index (BMI) to BNP levels was studied and it was found to be inversely correlated[4].

Evaluation and correlation of BNP and $HbA_1c$ would have been beneficial to understand the utility of these investigations for screening and management of heart failure and T2DM.

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