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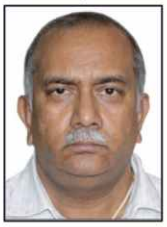

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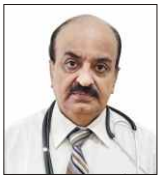
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Editorial

Advancements in Diabetes Mellitus Treatment — A Moment of Urgency and Opportunity as India Marks World Diabetes Day, 14 November, 2025

As India prepares to mark **World Diabetes Day** on **14 November, 2025**, the country faces a paradox: unprecedented scientific progress in the prevention and treatment of diabetes sits alongside an ever-growing epidemic of disease. India remains one of the nations with the largest absolute burden of diabetes in the world — the International Diabetes Federation (IDF) estimates nearly 90 million adults living with diabetes in India in recent years, and global prevalence continues to climb. This “diabetes capital” label is not merely rhetorical; it is a clarion call that demands we both celebrate therapeutic advances and confront the public-health, socioeconomic and ethical challenges that accompany them.

This editorial examines the major therapeutic advances of the last few years — in pharmacology, immunotherapy, regenerative medicine, and diabetes technologies — and places them in the Indian context. My aim is pragmatic: to sketch where modern diabetes care is heading, assess what is realistic and scalable for India, and suggest an evidence-informed pathway so that scientific breakthroughs translate into meaningful health gains for our population.

The Therapeutic Landscape : from Glucose-centric Care to Cardio-renal-metabolic Stewardship

For many decades diabetes care focused narrowly on glucose control. In the last 10-15 years — and accelerating now — treatment goals have broadened: we aim not only for safer glycemic targets but also for preservation of pancreatic function, prevention of cardiovascular and renal complications, weight management, and quality of life. Two interlocking forces underlie this paradigm shift: (1) drugs discovered or repurposed for pleiotropic benefit (eg, SGLT2 inhibitors and GLP-1 receptor agonists) and (2) precision technologies that tailor insulin delivery and monitoring to physiological needs.

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors, initially developed for glycemic control, have now an established role in reducing heart failure hospitalizations and slowing progression of chronic kidney disease — benefits that extend beyond glycemia. Similarly, incretin-based therapies — GLP-1 receptor agonists — have reshaped treatment by improving glycemic control, producing sustained weight loss, and delivering cardiovascular risk reduction in many patient groups. The therapeutic effect-size for weight and metabolic outcomes achieved with newer agents has been nothing short of transformative for selected patients.

The arrival and maturation of dual and multi-agonists : tirzepatide and the obesity-diabetes nexus

Perhaps the most discussed pharmacologic advance in recent years is the advent of dual incretin agonists — molecules that simultaneously target GLP-1 and GIP

receptors (and in trials, sometimes additional pathways). Tirzepatide, a dual GIP/GLP-1 agonist, has produced dramatic reductions in both glycated hemoglobin and body weight in randomized controlled trials. Recent head-to-head and longer-term data published in high-impact journals show that tirzepatide offers superior weight loss and metabolic benefits compared with earlier GLP-1 monotherapy in many patients, and it has opened a new line of thinking: treating obesity as a core therapeutic target to prevent and manage type 2 diabetes. These data hold particular importance for India, where the phenotype of diabetes is heterogeneous and where visceral adiposity and ectopic fat deposition contribute importantly to disease risk spectrum.

However, pharmacology's promise raises practical and ethical questions. These agents are costly, side effects (principally gastrointestinal) can be limiting, and global demand has stressed supply chains. The FDA and other regulators have also recently warned about unapproved formulations and online vendors peddling spurious 'GLP-1' products — a patient-safety issue that demands vigilance from clinicians and policy-makers alike. For India, responsible adoption requires negotiated pricing, local regulatory oversight, and clear clinical guidelines that prioritize those most likely to benefit.

Disease Modification for Type 1 Diabetes : Immunotherapy and the Promise of Delaying — or Preventing — Clinical Onset

Type 1 diabetes (T1D) is no longer perceived as inevitably progressive and untreatable. Immunotherapies designed to modulate or delay autoimmune destruction of β-cells now show clinically meaningful results. Teplizumab, an anti-CD3 monoclonal antibody, has been the first therapy to demonstrate a delay in progression from stage 2 (autoimmunity with dysglycaemia) to stage 3 clinical T1D in high-risk individuals. While teplizumab does not cure T1D, it offers a model for secondary prevention — identifying at-risk people through screening and delaying symptomatic disease. In the long run, this strategy could reduce early life burden, limit hospitalizations for diabetic ketoacidosis, and shift long-term complications curves.

Translating immunotherapy into routine practice in India will require strengthening of screening programs (for islet autoantibodies), building pathways for genetic and immunologic risk stratification, and ensuring cost-effectiveness analyses that incorporate Indian demographics and healthcare costs. Ethical considerations about identifying at-risk children who may never progress (and the psychosocial impact of labeling) must be addressed sensitively.

Regenerative Medicine and Cell Therapy: Islet Replacement Moves from Bench toward bedside

Regenerative approaches — particularly stem cell-derived islet transplantation — have advanced dramatically. Investigational products (for example, Vertex's VX-880/Zimislecel and related products) are showing promising early-phase results: engraftment of insulin-producing cells derived from stem cells has, in some trial participants, reduced or even eliminated exogenous insulin requirements. These results, while preliminary and from carefully selected cohorts, represent the first convincing signals that restoration of endogenous insulin production at scale might become possible in the coming years.

Yet the road to broad availability is complex. Cell therapies raise questions of long-term durability, immunosuppression requirements, manufacturing capacity, cost, and regulatory frameworks — all the more challenging in a resource-limited health system. India should invest in translational research capacity and participate in global consortia so that these therapies, if validated, are accessible to its population rather than remaining available only in high-income settings.

Technologies that close the Loop : CGM, Pumps and Automated Insulin Delivery

Diabetes technology has matured from sporadic self-monitoring to continuous, often automated, systems. Continuous Glucose Monitors (CGMs) provide near real-time glucose readings and trend information and have been shown to reduce hypoglycemia and improve time-in-range. Insulin pumps combined with sophisticated algorithms form hybrid or fully closed-loop systems (the so-called "artificial pancreas"), which adjust basal insulin delivery frequently based on CGM inputs. Systems such as the MiniMed™ 780G and other automated insulin delivery systems now routinely demonstrate improved time-in-range and reduced hypoglycemia in people with type 1 diabetes.

From an Indian perspective, CGM and pump technologies offer game-changing clinical benefits but are limited by cost, supply, and the need for technical support. Pragmatic strategies that could increase access include government tendering for bulk procurement, local manufacturing of consumables, training programmes for allied health professionals in pump and CGM management, and tiered reimbursement models that prioritize the most vulnerable and those at highest risk of severe hypoglycemia.

Cardiometabolic Outcomes and Kidney Protective Therapies : Changing the Prognosis

The last decade has seen therapies that not only lower blood glucose but demonstrably reduce cardiovascular and renal events — the main drivers of diabetes-related morbidity and mortality. SGLT2 inhibitors reduce heart failure hospitalizations and slow chronic kidney disease progression, while some GLP-1 receptor agonists reduce major adverse cardiovascular events. These outcomes data have compelled international guideline committees to recommend tailored therapy based on comorbidities rather than simply starting with metformin for everyone.

For India — where cardiovascular disease and diabetic kidney disease constitute major burdens associated with diabetes — integration of these agents into care pathways could change prognosis at population scale. That said, broad adoption will require policy action to make these drugs affordable and available in public health programmes; inclusion in essential medicines lists; and training clinicians to use these agents appropriately, including monitoring for adverse effects and managing polypharmacy.

Preventive Strategies, Screening and the Role of Weight Management

Pharmacologic advances must be paired with effective prevention. Agents like tirzepatide have shown not only glycemic benefits but also significant reductions in progression from prediabetes to diabetes in trial populations — suggesting that pharmacologic prevention alongside lifestyle measures could be a powerful tool. But prevention at national scale will still hinge on population-level interventions: urban planning that supports physical activity, taxation and regulation of unhealthy foods and sugar-sweetened beverages, school-based nutrition programs, and community-level screening with appropriate referral pathways.

India's public health architecture must prioritize early detection and prevention: opportunistic screening in primary care, simple risk-score tools integrated into community health worker workflows and targeted interventions for high-risk groups. These are low-cost strategies with the potential for high yield if tied to clear referral and incentive structures.

The Health Systems Challenge : Equity, Access and Affordability

No advance in pharmacology or technology is meaningful if it is unavailable to the majority. New drugs and devices are expensive. Without carefully designed policy interventions, we risk widening disparities: a two-tiered system where affluent patients access the latest therapies while the majority rely on older, less effective treatments.

Practical measures India should consider include: negotiating volume-based pricing with manufacturers; stimulating domestic production of biosimilars, GLP-1 analogues and pump consumables; public procurement for high-risk groups; incorporating high-value diabetes medicines and technologies into public insurance schemes; and strengthening the supply chain to prevent stockouts. Additionally, clinician stewardship is essential — selecting patients who derive the most absolute benefit, avoiding off-label use and preventing inappropriate use driven by social media hype.

Real-world Safety, Misinformation and Pharmacovigilance

The extraordinary demand for GLP-1–class drugs and related agents has created a parallel market for unregulated preparations and online vendors selling unapproved products. The regulatory warnings from agencies like the US FDA about unapproved GLP-1 products underscore the need for robust pharmacovigilance and patient education. India's regulators and clinician bodies must be proactive: monitoring adverse events, issuing clear guidance on approved formulations, and educating the public to avoid unsafe products.

Primary Care and Task-shifting : The Manpower Imperative

Managing diabetes at population scale requires decentralization. Specialist endocrinologists cannot deliver care for tens of millions alone. Strengthening primary care through education, decision-support tools, simple algorithms for medication intensification, and task-sharing with trained nurses and community health workers will be essential. Telemedicine can support remote mentoring and continuity, but it must be integrated with in-person services for screening, vaccinations, foot care and urgent complications.

India has strengths to build on: a dense network of primary centers, a large cadre of community health workers, and an expanding digital health ecosystem. The challenge is to align incentives, ensure continual training, and embed quality metrics — such as time-in-range, blood pressure and albuminuria screening — in routine practice.

Research, Registries and an Indian Evidence Base

Most pivotal clinical trials have been conducted in high-

income countries. While global evidence is invaluable, India needs domestic research to answer context-specific questions: differential drug responses in Indian phenotypes, cost-effectiveness in constrained budgets, implementation science on how to scale CGM and insulin delivery, and long-term outcomes of immunotherapy and cell therapy in our population. National registries for diabetes complications, CGM/pump use, and immunotherapy outcomes would provide real-world evidence to guide policy and practice.

Ethical, Social and Psychosocial Considerations

A focus on technologies and drugs should not eclipse the person living with diabetes. Screening children for autoantibodies or prescribing disease-modifying therapies involves psychosocial consequences. Weight-management drugs have benefits and side effects — and their popularity has societal implications for body image and equity. Clinicians must practice compassionate communication, shared decision-making and ensure that interventions respect patient autonomy and cultural contexts.

Call to Action for Clinicians, Researchers and Policy-makers

As we celebrate World Diabetes Day 2025, the message for stakeholders is threefold :

Adopt innovations rationally — Embrace therapies and technologies that demonstrate hard clinical benefit (reduced cardiovascular events, renal protection, meaningful reduction in insulin needs) while stewarding resources and prioritising equity. Use risk-based approaches to select patients most likely to benefit, and develop national clinical guidelines that reflect resource realities.

Invest in prevention and early detection — Scale opportunistic and community screening, invest in school- and workplace-based prevention programmes, and integrate obesity management into standard care pathways. Consider targeted pharmacologic prevention for very high-risk individuals when cost-effective.

Strengthen systems and capacity — Expand primary care capability for diabetes management, negotiate affordable pricing and domestic production where feasible and build registries and pharmacovigilance systems to monitor real-world outcomes and safety.

The Clinician's Role : Balancing Innovation with Pragmatism

For practicing physicians in India, the coming years will demand clinical judgment that balances innovation with pragmatism. New agents like tirzepatide and other dual agonists can be transformative for selected patients — those with obesity, high cardiometabolic risk, or significant burden from hyperglycaemia — but they will not be the right choice for everyone. In resource-limited settings, older medicines (metformin, SGLT2 inhibitors for cardiorenal indications, and safe insulin protocols) remain central. The art of medicine will be to use new tools where they deliver greatest marginal benefit, while ensuring that fundamental elements of care — blood pressure control, lipid management, foot care, vaccination and education — are universally delivered.

Conclusion : Hope Coupled with Responsibility

The scientific advances in diabetes treatment over the past few years give us cause for cautious optimism. Pharmacologic breakthroughs, disease-modifying immunotherapies, regenerative cell-based strategies, and automated technologies together outline a future in which diabetes is not merely managed but its trajectory altered. Yet India's enormous burden of disease means we must be intentional: translating cutting-edge science into public health impact requires policy leadership, equitable financing, workforce transformation, and culturally appropriate patient engagement.

On this World Diabetes Day, we should celebrate scientific progress while reaffirming collective responsibility. India can — and must — move from being the diabetes capital in the sense of burden, to a leader in delivering equitable, evidence-based diabetes care. To do so will require sustained collaboration among clinicians, researchers, industry, patient groups, and policymakers. If we align innovation with equity, the gains of our laboratories and clinical trials can become the health of our people.

Further Reading

1 International Diabetes Federation — data on India and global Diabetes Atlas (2024-2025).
2 NEJM: Comparative data on tirzepatide vs semaglutide (2025).
3 New England Journal of Medicine
4 Reviews on GLP-1 biology and expanding clinical role of incretin-based therapies.
5 Teplizumab and T1D disease-modifying therapy literature and reviews (2022-2025).
6 Vertex / VX-880 / Zimislecel early data on stem cell-derived islet therapies (2024-2025).
7 Technology sources: Medtronic MiniMed™ 780G and automated insulin delivery system information (2024-2025).
8 Safety/regulatory alerts about unapproved GLP-1 products and online vendors (regulatory/press reports).

Hony Editor, JIMA **Kakali Sen**

Original Article

To Estimate and Compare the Prevalence of Fibromyalgia among Health Care Personals Working in Tertiary Care Centre of North India

Anjana Pandey[1], Ajay K Maurya[2], P K Maheshwari[3], Akhilesh Kumar Singh[4], Nikhil Pursnani[5], Ashish Gautam[4], Prabhat Agrawal[6]

Abstract

Background : The prevalence of the Fibromyalgia syndrome in the health care worker is considerable and constitutes a significant health care issue.

Aims and Objective : To estimate and compare the prevalence of fibromyalgia among health care personals working in Tertiary Care Centre of North India.

Materials and Methods : This cross-sectional prevalence study involved 377 adults of age group of 18-40 years at Tertiary Care Centre of North India over a period of one and half years. Study population included Undergraduates, Interns, non-clinical and Clinical Departments Junior Residents, fulfilling 2016 modification of 2010 American rheumatology criteria for diagnosis of Fibromyalgia. Consent was taken from all the participants. All participants were subjected to fibromyalgia questionnaire and interpretations were made.

Result : Overall prevalence of Fibromyalgia among hospital workers was 3.98%. Prevalence among female (5.73%) was more as compared to male (3.14%). Among MBBS students, prevalence was 2.94%.and in interns it was 3.51%. Prevalence among Non-clinical and Clinical Junior Resident of several department were 4.34% and 5.30 % respectively.

Conclusion : Fibromyalgia syndrome is common in health care workers and is associated with other comorbidities like headache, fatigue, IBS and migraine.

Key words : Fibromyalgia, 2016 modification of 2010 American rheumatology criteria, Health care workers.

Fibromyalgia is a rheumatic condition characterized by muscular or musculoskeletal pain with stiffness and localized tenderness at specific points on the body. Fibromyalgia is often associated with sleep disorders, fatigue, somatic and cognitive symptoms, as well as psychic disorders more common in females[1-3]. The primary symptoms of Fibromyalgia, wide spread pain and fatigue, can be found in many medical disorders. Similarly, Fibromyalgia can co-exist with other medical conditions[4-6]. The proper approach to avoid misdiagnosis is to ascertain the presence or absence of Fibromyalgia and then to determine whether other disorder with widespread pain and fatigue are present.

The diagnosis of Fibromyalgia is made in patients who present with persistent, widespread, and generalized pain who are otherwise normal on physical examination by assessing patients on various parameters incorporated in the (2016) modification of 2010/2011 American rheumatology criteria for diagnosis of Fibromyalgia[7]. This revision combines Physician and questionnaire criteria, minimizes misclassification of regional pain disorders and eliminates the previously confusing recommendation regarding diagnostic exclusions. The physician-based criteria are valid for individual patient diagnosis. The changes to the criteria allow them to function as diagnostic criteria, while still being useful for classification[7]. Fibromyalgia may now be diagnosed in adults when all the following criteria are met:

(1) Generalized pain, defined as pain in at least 4 of 5 regions, is present.

Editor's Comment :

- Medical professionals with fibromyalgia should learn to adapt their work environment, prioritize self-care and symptom management, develop coping strategies for chronic pain and fatigue and seek support to maintain their well-being and continue delivering quality patient care.

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(2) Symptoms have been present at a similar level for at least 3 months.

(3) Widespread pain index (WPI) ≥7 and Symptom Severity Scale (SSS) score ≥5 OR WPI of 4-6 and SSS score ≥9.

(4) A diagnosis of Fibromyalgia is valid irrespective of other diagnoses. A diagnosis of Fibromyalgia does not exclude the presence of other clinically important illnesses.

Aims and Objective

To study prevalence of Fibromyalgia among health care personals working in Tertiary Care Centre of North India.

Material and Methods

This prospective, cross-sectional, observational study was conducted in a Tertiary Care Hospital of Northern India after ethical approval and subject consent over a period of one year ie, from March, 2017- August, 2018 & May, 2010. Total 377 health care workers of both sexes of age group ranging from18-60 years both from various Clinical and Non-clinical Departments, fulfilling 2016 modification of 2010 American rheumatology criteria for diagnosis of Fibromyalgia were enrolled. All participants were subjected to Fibromyalgia questionnaire and interpretations were made.

Modified 2010 ACR diagnostic criteria self-assessment questionnaire was provided to the patients. Patient was made to fill a self-report questionnaire before he / she entered examining Physician's chamber. The questionnaire was divided into 3 sections. The first section assessed the distribution of body pain using the same 19 body areas as in the WPI, patients marked each area either "yes" or "no" to indicate the presence or absence of pain or tenderness in that area over the past week. Patient scored 1 point for each painful or tender body area, yielding a self-report WPI score between 0 and 19, analogous to the WPI score in the Physician-assessed diagnostic criteria. The second section evaluated the severity of problems with daytime fatigue, no restorative sleep and cognitive dysfunctions (trouble thinking and remembering) using separate questions and scores given.

The third section asked patients whether they experienced pain or cramps in the lower abdomen, depression, or headache during the past 6 months, for every positive answer patient scored 1.

Scores from the second and third sections were summed up to yield a 0-12 SS Scale score analogous to the SS Scale score in the physician-assessed diagnostic criteria. Scores from the WPI and SS Scale sections were summed up to yield a 0-31 index termed as Polysymptomatic Distress Scale (PSD). Patients with a PSD scale score of 13 or more were diagnosed with Fibromyalgia provided, the symptoms have been present at a similar level for at least past 3 months and the patient did not have any other disorder that would otherwise explained the symptoms.

Observation

Overall prevalence of Fibromyalgia among hospital workers was 3.98%. Prevalence among female (5.73%) was more as compared to Male (3.14%). This study included 170 MBBS students (45.05%), 132 junior residents from clinical departments (35.01%) and 46 Junior Residents from Non-clinical Departments (12.20%). Among MBBS students, prevalence was 2.94%.and in Interns it was 3.51% (Table 1). Prevalence among Non-clinical and Clinical in which we included Junior Resident from several department were 4.34% and 5.30 % respectively (Table 2).

Some other condition such as Depression, Stress, IBS, Migraine are related to Fibromyalgia. Out of 15 subjects in which who fulfilled the 2016 modification

Table 1 — *Designation wise prevalence*

Designation	Total		Affected		Prevalence of FM
	No	%	No	%	
Undergraduates (MBBS)	170	45.09	5	53.33	2.94%
Interns	28	7.42	1	0.00	3.51%
Postgraduates					
Clinical	132	35.01	7	46.67	5.30%
Non-clinical	46	12.20	2	0.00	4.34%
Total	377	100.00	15	100.00	3.97%

Table 2 — *Prevalence among Clinical and Non clinicals Resident Doctors*

Designations	Total	Affected	Prevalence
Clinical	132	7	5.30%
Others {Undergaduates (MBBS) +Interns+Non-clinicals resident doctors}	245	8	3.26%
Total	377	15	3.97%

of 2010 American rheumatology criteria for Fibromyalgia, 7 subjects (46.67%) diagnosed as depression whereas if we compare the overall prevalence of depression in 377 subjects, it was 7.6% it showed depression was strongly associated with Fibromyalgia. Other factors such as Fatigue (40%), IBS (33.3%) and Migraine (40%) were also related with Fibromyalgia (Table 3).

Table 3 — *Other symptoms related to fibromyalgia*

	Not affected (N=377)		Affected (N=15)	
	No	%	No	00.00%
Depression	16	4.24	7	46.67
Fatigue	24	6.36	6	40.00
IBS	42	11.14	5	33.33
Migraine	37	9.81	6	40.00

Discussion

As we moved from MBBS, Intern, Non-clinical to Clinical Resident Doctors, prevalence also increased. Several factors affected the varied prevalence rate among various groups but there were two main factors responsible for this difference, first increasing age and second is long working hours resulting into continuous increase in stress levels. This study very clearly interpreted higher prevalence in Junior Residents Working in Clinical Departments. Probably this was attributed to time pressure, rigorous work schedule, erratic sleep schedule, high self-imposed expectations and high expectations from seniors as well as from patients, delayed gratification, limited control and a loss of autonomy, conflict between career and family, feelings of isolation, as well as research and teaching activities. FM were two to seven times more likely to have one or more of the following comorbid conditions: Depression, Anxiety, Headache, Irritable Bowel Syndrome, Chronic Fatigue Syndrome, Systemic Lupus Erythematosus and Rheumatoid Arthritis. All the above factors probably have led to increased prevalence of fibromyalgia alone or in association with comorbidities like Fatigue, depression, IBS and Migraine in Health Care workers.

Conclusion

The prevalence of the Fibromyalgia syndrome in the health care worker is considerable and constitutes a significant health care issue. It is desirable and important to have more nation-wide epidemiological studies on FM to have a better view of the prevalence of this disorder Worldwide, and to measure the burden of FM on health care persons. Our findings underline the possibility that work-related stress may play a major role in the development of FM symptoms among individuals working as Health Care Worker.

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Conflict of Interest : None

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Original Article

A Case Control Study of COVID-19 and its Association with Antibody Titre

Sangita Patel[1], Reetika Ranjan[2], Sonal Mishra[3], Greenam Tarani[2], Jesal Patel[4]

Abstract

Background : Antibodies are detected in the blood of people who are tested after infection; they show the body's efforts to fight off a specific infection.

Aims and Objectives : To know the difference in the antibody titre between cases and control. To correlate the time interval between development of disease and antibody titre test and the number of days of symptoms with antibody titre in COVID-19 positive participants

Materials and Methods : A case control study was done at University Health Centre of the Maharaja Sayajirao University of Baroda. SARS CoV-2-specific IgG antibody titre was measured in 100 case and 100 controls. Correlation coefficient and chi square test was applied for statistical analysis.

Result : 82% cases and 36% controls were seropositive for IgG Ab titre against COVID-19.97% cases had mild symptoms and only 3% had moderate symptoms. The mean and SD of symptoms was 8.4 days (SD-6.7). The correlation between time interval of development of disease and Ab titre test done with antibody titre was found to be inverse with r=-0.3810, P=0.0001, (95%CI = -0.5372 to -0.1995). The correlation between number of days of symptoms present with antibody titre was positive with r= 0.2254, P=0.0242, (95% CI= 0.03029 to 0.4039).

Conclusion : About one-third of controls were seropositive for IgG antibody titre against COVID-19 without any sign and symptoms of COVID-19. The correlation between time interval of development of disease and Ab titre test done with antibody titre was inverse with low negative correlation and negligible correlation was found between number of days of symptoms with antibody titre.

Key words : Case Control Study, Antibody Titre, IgG, COVID-19, Symptoms.

COVID-19 is the disease caused by a new Corona virus called SARS-CoV-2. WHO first learned of this new virus on 31 December, 2019[1].

Antibodies are detected in the blood of people who are tested after infection; they show the body's efforts to fight off a specific infection. In general, a positive antibody test is presumed to mean a person has be eninfected with SARS-CoV-2, the virus that causes COVID-19, at some point in the past. Antibodies usually start developing within 1 to 3 weeks after infection[2].

Antibodies to SARS-CoV-2 demonstrate infection when measured at least 14 days after symptom onset[3].

Two studies published demonstrate that COVID-19 immune-responses last as long as 8 months, although the authors focus on different reasons. The first study, published in *Science Immunology*, followed as mall cohort of Australians from day 4 to day 242 after infection. All patients demonstrated the presence of memory B-cells, immunecells that "remember" viral proteins and can trigger rapid production of antibodies when re-exposed to the virus as long as 8 months safter initial infection. The second study investigated antibody responses in 58 confirmed COVID-19 patients in South Korea 8 months after asymptomatic or mild SARS-CoV-2 infection, finding high rates of serum antibodies. These results, published in *Emerging Infectious Diseases*, are contradictory to both the first study's antibody data and previous research that showed antibodies waning after 20 days, but theauthors suggest that variations in immunoassay test characteristics and manufacturing may be responsible for the difference[4].

Editor's Comment :

- Asymptomatic infections are common in COVID-19.
- As the duration of illness increases, the antibody titre decreases.
- Immunity is attained as a result of COVID-19 infection.

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Aims and Objectives

(1) To know the difference in the antibody titre between cases and controls.

(2) To correlate the time interval between development of disease and antibody titre test with antibody titre in COVID-19 positive participants.

(3) To correlate the number of days of symptoms with antibody titre in COVID-19 positive participants

Material and Method

A case control study was carried out at University Health Centre of the Maharaja Sayajirao University of Baroda. The study was conducted among residents of University campus including staff members and students studying and residing at university. Those who were COVID-19 positive and minimum 30 days have elapsed from the date of RTPCR/RAT testing were selected as cases. Those who were COVID-19 test negative or those who had never tested for COVID-19 and never developed any COVID related symptoms were selected as controls.

Each participant was explained the purpose of the study and only those who signed the consent form was included in the study. Blood sample for IgG antibody titre was collected by a trained laboratory technician. Total study duration was 13 months, January, 2021 to January, 2022. The blood sample was collected solely for the purpose of measurement of IgG antibody of COVID-19. Report of each participant was given and explained to them.

Out of 200 participants, 100 were cases and 100 were controls. Pilot study was done for calculation of sample size. In this pilot study, the Odds of having antibody in COVID-19 positive patients was 3 times higher as compared to non-COVID-19 patients. At 95% CI with power-90%, ratio of cases and controls was 1:1, proportion of exposure in control-20% and in case -42% and using Open Epi software[5] the sample size came 100 in each group. So, we took sample size of 100 cases and 100 controls.

Questionnaire : Apre-tested,semi-structured questionnaire was used to collect data on COVID-19 diseasere garding Socio-demographic details of the participants, co-morbidity of the patients, knowledge of hand hygiene, social distancing, any ayurvedic medicine or homeopathic medicine intake, chemoprophyl axis of HCQ, visit to public places like hotels, malls, parks, had been in social gatherings like party, marriage, any travel history outside city, state or country, the manner, place and type of masks used by them.

Analysis

Data entry was done in Microsoft Excel 2007 and analyzed by using MedCalc software version 12.5.0.0[6]. Descriptive analysis was used to describe the distribution of all variables in cases and control group. Odds ratio was calculated for presence of specific SARS CoV-2 IgG antibody among cases and controls with 95% confidence interval. Correlation was assessed for the time interval between development of disease and antibody titre test with antibody titre in COVID-19 positive participants. Correlation was also assessed for the number of days of symptoms with antibody titrein COVID-19 positive participants. Correlation coefficient was calculated for the same. Chi square was calculated to see the significance of factors associated with presence of antibody in controls.

Ethics : The study was approved from the Ethical Institutional Ethics Committee for Biomedical and Health Research (IECBHR) of the institute. After explaining the participants in their local language about the study, its purpose and confidentiality of information a written consent was taken from them before starting interview.

Data Confidentiality : The study participants were assured that the information they shared would be kept strictly confidential and would be used only for research purposes and underno circumstances was shared with anyone in a manner which could identify any of the participant.

COVID-19 antibody IgG was measured by fully automated 2-step sandwich immuno-assay using indirect chemiluminescent technology (<1.0 index is non-reactive and ≥1.0 index is reactive).

Observations

200 (100 cases and 100 controls) participants (mean age and SD of cases - 42.97±15.91 years, controls-37.53±14.52 years) were included. Among cases 46% were males and among controls 43% were males. 68% cases and 44% controls were educated more than or equal to graduation (Table 1).

Table 2 showed, there was statistically significant difference observed in education (p-value- 0.042),

Table 1 — *Socio-demographic profile of the participants (N=200)*

Variables	Case (n=100)	Control (n=100)	Total (n)(%)
Age group (years) :			
>45 years	49	28	77(35.5%)
≤45years	51	72	123(61.5%)
Age (Mean ± SD)	42.97±15.91	37.53±14.52	
Gender :			
Male	46	43	89(44.5%)
Female	54	57	111(55.5%)
Education :			
More than or equal to Graduation	68	44	112(56%)
Less than Graduation	32	56	88(44%)
Occupation :			
Business / self employed	5	8	13(6.5%)
Government service	46	42	88(44%)
Private service	8	6	14(7%)
Home maker and retired	24	21	45(22.5%)
Student	17	23	40(20%)

travel history (p-value- 0.0064), mask use (p-value- 0.0010), technique of wearing mask (p-value- 0.182), knowledge of hand hygiene (p-value- 0.0032) between two groups of controls, one with antibody titre present (n= 36), and other with no antibody titre (n=64).

Out of 100 cases 82 cases were seropositive and 18 cases were seronegative for COVID-19 IgG antibody and among controls 36 were seropositive. The crude odds ratio was 8.09 which shows that the odds of antibody presence in cases was 8 times more in comparison to controls, with CI=4.21-15.56. We found χ^2=43.73 and p-value=<0.0001, which shows that this association was statistically significant (Table 3).

97% cases had mild symptoms and only 3% had moderate symptoms. The mean and SD of symptoms was 8.4 days (SD-6.7).

Table 4 shows that 73% cases of COVID-19 had fever as presenting complain, 33% had fatigue. Loss of taste and smell was present in 30% patients of COVID-19, cough in 26%, Sore throat in 22%. 18%, 13% and 10% had experienced myalgia, diarrhoea and rhinorrhoea respectively. Breathlessness was present in 10% of cases.

6 out of 100 cases were asymptomatic. In 2 patients had symptoms which lasted for about 30 days complaining loss of taste and smell and fatigue as symptoms which persisted for long time.

The correlation between time interval of development of disease and Ab titre test done with antibody titre was found to be inverse with r= -0.3810, P=0.0001, (95%CI=-0.5372 to -0.1995). This means that with increase in duration there was decrease in antibody titre, which showed that the finding was statistically significant.

Table 2 — *Factors associated with antibody presence among controls*

Parameters	Antibody present n=36(%)	Antibody absent n=64(%)	χ^2	p-value
Age (in years) :				
>45	12 (33.33%)	16(25%)	0.793	0.372
≤45	24 (66.67%)	48(75%)		
Gender :				
Male	23 (63.89%)	34(53.12%)	1.089	0.2966
Female	13 (36.11%)	30(46.88%)		
Education :				
More than or equal to Graduation	11 (30.56%)	31(48.43%)	4.126	0.042
Less than Graduation	25 (69.44%)	33(51.56%)		
Travel History :				
Yes	8 (22.22%)	32(50%)	7.407	0.0064
No	28 (77.78%)	32(50%)		
Visit outside the home :				
Never/sometimes	13 (36.11%)	21(32.81%)	0.1117	0.7381
Daily	23 (63.89%)	43(67.19%)		
Social gathering :				
Yes	11 (30.56%)	18(28.13%)	0.0661	0.7970
No	25 (69.44%)	46(71.87%)		
Mask use :				
Regular	25 (69.44%)	61(95.31%)	10.746	0.0010
Irregular	11 (30.56%)	3(4.69%)		
Technique of wearing mask :				
Correct	29 (80.56%)	61(95.31%)	5.5748	0.0182
Incorrect	7 (19.44%)	3(4.69%)		
Knowledge of hand hygiene :				
Correct	20 (55.56%)	53(82.81%)	8.684	0.0032
Incorrect	16 (44.44%)	11(17.19%)		
Maintaining social distance :				
Yes	30 (83.33%)	61(95.31%)	2.706	0.099
No	6 (16.67%)	3(4.69%)		
Self-medication of homeopathic or ayurvedic medicine :				
Yes	3 (8.33%)	4(6.25%)	0.0003	0.9869
No	33 (91.67%)	60(93.75%)		
Home remedies :				
Yes	9 (25%)	13(20.31%)	0.295	0.587
No	27 (75%)	51(79.69%)		
HCQ prophylaxis :				
Yes	1 (2.78%)	4(6.25%)	0.0822	0.774
No	35 (97.22%)	60(93.75%)		
Comorbidity :				
Yes	6 (16.67%)	17(26.6%)	1.274	0.2590
No	30 (83.33%)	47(73.4%)		

Table 3 — *Status of antibody presence in cases and controls (n same as percentage as n= 100 for both cases and controls)*

Antibody	Cases (100)	Controls (100)	Total
Present	82	36	118 (59%)
Absent	18	64	82 (41%)

OR = 8.09, CI = 4.21-15.56, χ^2 = 43.73, p-value = <0.0001

After categorizing the participant of COVID-19 into 3 groups according to time interval of development of disease and Ab titre test done.

A=<90 days; B=90-180 days; C=>180 days. We

Table 4 — *Cases present with specific symptoms*

Symptoms	Number of cases (n=100)
Fever	73 (73%)
Fatigue	33 (33%)
Loss of taste and smell	30 (30%)
Cough	26 (26%)
Sorethroat	22 (22%)
Myalgia	18 (18%)
Diarrhoea	13 (13%)
Rhinorrhoea	10 (10%)
Breathlessness	10 (10%)
Expectoration	03 (03%)
others	10 (10%)
Asymptomatic	06 (06%)

*Multiple answers possible

observed the mean and SD of titre level in each group to be A(n=53)=11.9(SD-10.3); B(n=25)=11.4(SD-10.0); C(n=21)=2.4(SD-3.5).

The correlation between number of days of symptoms present with antibody titre was positive with r= 0.2254, P=0.0242, (95% CI= 0.03029 to 0.4039). This means that with increase in number of days of symptoms, there was increase in antibody titre. This shows that the finding was statistically significant.

Discussion

This study proposed to determine the antibody titre difference in cases and controls, correlation of time interval of disease development and antibody titre test done with antibody titre in COVID-19 positive patients and correlation of number of days of symptoms with antibody titre in COVID-19 positive patients.

In our study we had taken 100 cases and 100 controls. We found 36 participants among controls to be seropositive for COVID-19 antibody.

In the present study 82% COVID-19 patients were positive for IgG serum antibody to COVID-19 and 36% controls were also positive.

The reasons were irregular use of mask (11%), incorrect hand wash technique (16%) travel history (28%) and in correct maskuse technique (7%). They were exposed to Corona virus due to above mentioned reasons but were asymptomatic and produced antibody to COVID-19.

A study conducted by Caturegli G, MateriJ, Howard BM, Caturegli P showed similar result as 83.33% of cases of COVID-19 were positive for serum antibody but no control had serum antibody[3].

One study conducted in Ahmedabad by Shilpa Yadav, 21% of those who had recovered from COVID-19 were positive for IgG antibody titre while in our study 82% were positive for the same[7].

Similarly, a study was done in Karnataka by G. Babu which showed that 16.8% of post COVID19 patients were positive for IgG antibody titre wherein our study showed that 82% were positive for the same[8].

The correlation between time interval of development of disease and Ab titre test done with antibody titre was found to be inverse and statistically significant. It was observed that as time elapsed after infection with COVID-19 there was decrease in antibody titre.

A study conducted by Levi R, *et al* showed that the antibody response persists for at least 8-10 months[9].

After categorizing the participant of COVID-19 into 3 groups according to time interval of development of disease and Ab titre test done.

A=<90 days; B=90-180 days; C=>180 days. Here we had observed that the mean of antibody titre of group A and group B was similar equal to 11 and mean of antibody titre of group C was significantly low and it was around 2. It was observed that there was low level of antibody titre when sample was taken after 180 days had elapsed from the day of RAT/RTPCR positive for COVID-19.

A study was conducted by F Javier Ibarrondo, *et al* which showed that levels of antibody against COVID-19 decreases dramatically over 3 months of infection while in our study we had observed that levels of antibody decreases dramatically over 6 months of infection[10].

Initially we had planned to check the Ab titre for COVID-19 for each case at different points of time from the time of COVID-19 diagnosis (30-90 days, 90-180 days, >180 days). However due to ethical issues this could not be done as it was unethical to ask the cases to refrain from vaccination just for the purposes of this study.

In the present study, there was statistically significant positive correlation of number of days of symptoms with antibody titre which showed that with increase in number of days of symptom there would be higher serum antibody titre. In our study there was negligible correlation.

Similarly, a study conducted by Files J, *et al* showed that symptom duration correlates with S-specific IgG antibody (r = 0.4); there was low positive correlation[11].

A study conducted by Young MK, *et al* showed that

IgG antibodies were most positively correlated with days from symptoms onset with an r value of 0.4 while in our study there was positive correlation but with R value of 0.22[12].

In our study, we found that 73% had the chief complain of fever with second most common complain of fatigue and loss of taste and smell with 33% and 30% respectively. Cough was present in 26% of cases, diarrhea (13%) Sore throat (22%) and least common was expectoration in 3% of cases.

A study conducted in China by Guan W, *et al* the predominant symptom was fever as was present in 43.8% of the patients on admission but developed in 88.7% during hospitalization. The second most common symptom was cough (67.8%). Nausea or vomiting (5.0%) and diarrhea (3.8%) were uncommon[13].

Another study conducted in tertiary care of Delhi by Jugal Kishore *etal* observed fever (51.4%) as the most common complain of COVID-19 patients followed by cough (41.7%), breathlessness (28.1%),headache (25.2%) and nausea/vomiting (20.3%)[14].

The study was limited only to the University Health Centre, which represents patients visiting to that centre only. And due to fear of COVID-19 limited number of patients used to come. Those who had history of moderate orsevere COVID-19 and had any comorbidity avoid to come to health centre unless there was any emergency. Therefore, data for moderate and severe categories were missed, which could have improved the results.

The strength of the study was that we have quantified the actual IgG titre value of all the participants instead of doing only presence and absence of IgG antibody (seroprevalence).

Conclusion

82% cases and 36% controls were seropositive for IgG Ab titre against COVID-19.

Asymptomatic and healthy seropositive controls for COVID-19 IgG Ab, who were undetected may actas superspreaders for COVID-19. This highlights the need for continuation of self-protective measures like proper and regular mask wearing and maintaining social distance.

The correlation between time interval of development of disease and Ab titre test done with antibody titre was inverse with low negative correlation.

Negligible correlation was found between number of days of symptoms with antibody titre.

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Original Article

Teaching Pathology to Medical Students — Impact of Transition from Glass Slides to Digital Images

Prema Saldanha[1], Renuka Patil[2]

Abstract

Background : Teaching Pathology with the traditional glass slides has problems like fading of the slides, storage and breakage. Digitalisation of slides has many advantages. The images can be retrieved and studied anytime; they are effective in more objective assessment, as the field of study can be made uniform; the slides can be uploaded into the e-learning portal, and the slides (images) are permanent. This study was done to compare the effectiveness of teaching Pathology using glass slides against digital images.

Material and Methods : The study was started after IEC clearance. The slides of the selected topics were digitalised. The students were divided into three groups and were taught using glass slides/ images/ both slides and images, with cross over, followed by a test. Feedback was obtained on the satisfaction levels of the students and Faculty.

Results : Analysis of the learning process (performance in the class test), following these classes, varied from slight improvement to marked improvement. The test marks obtained were not statistically significant. The results were not conclusive as the topics were few, and other variables which need to be considered are the students' academic abilities and the difficulty level of the topics. Results of the feedback obtained on a 5-point Likert Scale showed a significant difference (p=0.002) among those who preferred digital to glass slides.

Conclusions : The feedback obtained from the students showed a significant difference among those who preferred digital to glass slides.

Key words : Pathology, Teaching, Digital Images.

Pathology provides a scientific foundation for clinical practice[1,2]. The learning of Pathology is the first introduction to the understanding of human disease processes[1]. Pathology is a subject that is based in part on histopathologic examination of tissues which is important to understanding basic mechanisms of disease[1]. It is the medical discipline connecting morphological changes to clinical aspects. Therefore, the knowledge and study of pathology is essential for the understanding of clinical subjects[2].

The microscope has been the most widely used instrument in pathology education and is still the mainstay in the classroom[1]. In pathology education, there are shortcomings in the use of traditional microscopy. The major ones include the need for producing multiple glass slides from limited tissues for individual viewing by a large number of students; replenishment of slides for faded stains; broken or lost slides; and laboratory-bound access to learning[3].

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Editor's Comment :

- Use of Digital Pathology using slide scanners is not within the ambit of medical institutions in countries like India. Hence, use of static digital images capturing relevant fields is a suitable alternative for training Undergraduate students.
- This could also be used for training fresh Pathology Residents.
- It could also be implemented in other subject curricula as well as for preparing for the Postgraduate entrance exams.

Digital technology is ubiquitous and is an essential part of human existence today whether in a social, educational or professional arena[3]. The teaching of pathology is undergoing a digital revolution enabled by digital/virtual microscopy that has demonstrated a decrease in the use of traditional microscopes in medical education, both as a result of current developments in the curriculum as well as some disadvantages of the technique itself[1].

This study was done to compare the effectiveness of teaching Pathology using traditional glass slides against digital images and to record the perceptions among the Faculty & students.

Material and Methods

For this study, three major topics (each divided into

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two subtopics) which are taught in the practical classes were selected. The glass slides were studied and specific areas were selected. The microscopic images were converted into digital images using a microscope with attached camera. Multiple images were taken in scanner, low power and high power views, including all the relevant fields.

The 2nd year MBBS students who were studying Pathology, were divided into three groups: In the first group, the students were taught Practical Pathology using conventional microscopes using glass slides only. The second group was taught entirely using digital images. A few glass slides were kept focused for comparison. The third group, teaching was taught using glass slides along with digital images.

A cross over was done between the three groups using the same three topics. The teacher for a particular topic was the same for all the three groups to avoid bias and variation in the teaching. To assess the learning process, a test was conducted after these sessions and the performance was recorded.

Feedback on the perceptions (satisfaction survey) was obtained from the students and the Faculty involved in teaching using a 5 point Likert scale. The level of satisfaction/agreement was recorded as 1-Strongly disagree; 2-Disagree; 3-Neither agree nor disagree; 4-Agree; 5-Strongly agree. The results were analysed using the Chi-square test.

The feedback statements for the learning experience from the students included – Question (Q)1.I feel that digital slides were better than glass slides for learning; Q2.I feel that I was more interested in this type of practical class; Q3.I felt that I was more motivated to study after these practical classes; Q4.I felt that I learnt more with digital than glass slides; Q5.I feel that the clarity of images is better with digital slides: Q6. I would prefer similar practical classes in future and Q7. I prefer digital slides for the exam.

The Faculty experience feedback criteria included – Q1. I feel that digital slides were better than glass slides for teaching & learning; Q2. I felt that the students more engaged in the class; Q3.I felt that the students were more motivated to learn, Q4. I feel that the clarity of images is better with digital slides and Q5.I prefer to use digital slides for the exam.

The study was started after obtaining clearance from the Institutional Ethical Committee (IEC Protocol No 2019/140). As the students form a vulnerable group and may experience perceived coercion from their teachers to take part in the study, informed consent was taken from the students so that they know they have a voluntary choice to take part or refuse to take part in the study.

Results

The learning process as recorded by the performance in the class tests is given in Table 1.The values depict the number of students who identified the slides correctly against the total number of students who answered the test.

The perceptions were recorded from the feedback forms. All the Faculty (100%) agreed or strongly agreed that digital slides were better than glass slides. The feedback from the students is given in Table 2. There was a statistically significant difference among the students who preferred digital slides to glass slides (p=0.002).

Discussion

With the rapid acceleration in the use of computers in medical education, teaching pathology has taken a big turn in this century. Technology has been

Table 2 — *Results of the feedback from students obtained on a 5-point Likert Scale*

Question	Strongly agree/ Agree	Disagree/ Strongly disagree
1	75 (60%)	18 (15%)
2	80 (64%)	21 (17%)
3	68 (54%)	22 (18%)
4	73 (58%)	22 (18%)
5	101 (80%)	5 (4%)
6	80 (64%)	10 (8%)
7	96 (76%)	10 (8%)

Table 1 — *Analysis of performance in the test*

Classes		Teaching Methodology			Remarks of the performance
		Glass slides	Digital Images	Both slides & Images	
TOPIC 1	Subtopic 1	3/36 (8%)	25/43 (58%)	14/46 (30%)	Marked improvement
	Subtopic 2	29/36 (81%)	30/43 (70%)	31/46 (67%)	Slight improvement
TOPIC 2	Subtopic 1	33/46 (72%)	36/36 (100%)	30/43 (70%)	No change
	Subtopic 2	30/46 (65%)	35/36 (97%)	6/43 (14%)	Uncertain
TOPIC 3	Subtopic 1	20/43 (47%)	36/46 (78%)	36/36 (100%)	Improvement
	Subtopic 2	34/43 (79%)	39/46 (85%)	35/36 (97%)	No change

developed to photograph slides and store the images, which can be retrieved and studied anytime.

Technology for production of virtual slides was developed in 1985; however, it was not until the late 1990s that technology could be used to apply virtual microscopy to medical education[4,5]. Virtual Microscopy is being used in some parts of the USA, Europe and also in a few Middle East and Far East countries.

On completion of scanning, the pictures which are captured in millions of pixels, are blended together with the help of software to finally produce a composite picture which is an exact replica of the tissue section. The image thus created is automatically stored in the computer. The image is called digital slide or whole slide image or virtual image or e-slide and has the characteristics of the original section[6].

The digital slide can be viewed on the screen of the PC or laptop in any magnification just like a glass slide is viewed under the microscope and any area of the slide can be viewed.

Image can be annotated to point out salient features which are very useful for Undergraduate teaching[6].

The need for digital microscopy has arisen because of the several problems with traditional microscopy. These include, the need for producing multiple glass slides from limited tissues for individual viewing by a large number of students; replicating the same finding in all the sections; replenishment of slides for faded stains; broken or lost slides; difficulty in storage and laboratory-bound learning[3,6,7].

There are many avenues for implementation of Digital microscopy. Various studies have been done in teaching Undergraduate medical students, histology for first year students and histopathology for second year students. The current integrated and problem-based curricula make this innovative method of teaching a boon[4]. It has also been used for teaching dental students[9]. Postgraduate students in Pathology and Dermatopathology can also be trained by using virtual slides[2]. They can serve as slide repositories to be shared among Institutions[4]. Training and discussion of autopsy cases can be done and the slides of the cases can be stored permanently[2]. Digital pathology can also be utilised in proficiency testing in other fields of anatomic pathology and in cytopathology[1].

Virtual microscopy is being introduced into the Continuing Medical Educational (CME) and self-assessment programmes in many medical educational organisations. Virtual microscopy is very attractive to medical educators because it emulates the pan and zoom features of traditional microscopy, with the added advantages of the efficiency, accessibility and versatility of computer-assisted education[4].

The benefits of using digital slides are many. Digital images can be standardized, with the potential for image enhancement, so that all students will study the exact same tissue section· reproducing 100 or more slides showing just the same alteration is actually impossible. One perfect example can be converted to digital images[1,2,4]. With classes having a large number of students these days, sharing of the microscope and slide set is required[6].

In pathology postgraduate education, collections of rare cases can be made. Also slides of Immunohistochemistry, Immunofluorescence and Fluorescent in-situ Hybridisation (FISH) can be permanently stored. These stains are not long-lasting and are very expensive when it comes to making multiple sets. Fluorescent microscopes are also expensive[2].

Conventional microscope glass slides cannot be easily annotated with any precision, and rely on crude techniques like pen-marking/"dotting". Teaching is done by utilising an eyepiece with a pointer for highlighting a certain area in the field. Multiple annotations (arrows, circles, texts, etc.) can be placed exactly where needed in the digital images[1,2].

The time used for setting up the educational sessions and actual teaching process are much less compared to traditional microscopy[1].

The use of the microscopes is often limited to the working hours of the Departement. This requires the students to be physically present during these hours (lab-bound learning). With digital pathology study can occur wherever and whenever the student wishes to and encourages self-directed learning[1,4].

Storage and maintenance of microscopes and glass slides sets are cumbersome and require significant expenses. Digital images can be easily stored in in the computer which makes the retrieval easy[1].

This technology enabled the students to learn pathology in a more interactive and stimulating manner[1] as the slides can be integrated in the form of case-based studies. Curriculum reforms in medical education worldwide has focused on an emphasis on independent learning, and on the development of interpersonal skills and problem solving abilities[10].

Blake, *et al* (USA) describe how the histology course

for first-year medical students changed successfully from using glass slides and microscopes to using virtual slides and virtual microscopes. This study published in 2003 is thought to be the first report of a successful complete transition from the use of glass slides and microscopes to the combined use of static labeled images and virtual slides and virtual microscopes for the teaching of medical histology in North America[5].

Fonyad, *et al* (Hungary) have summarised the experiences gathered with the installation of a fully digitised histology lab for under graduate education. Student satisfaction questionnaire and a Tutor satisfaction questionnaire confirms the satisfaction and the acceptance of digital slides[2].

Lakhtakia, *et al* (UAE) studied the feasibility of achieving early integration of clinical reasoning with undergraduate pathology teaching on a virtual microscopy platform and to determine its student-centricity through student feedback. Most of the students agreed that the there was development of a strong clinical foundation. Integration and clinico-pathological correlation were found to be the strengths of this educational effort. High student attendance and improved assessment scores on critical thinking were observed. Easy access was a significant student-centric advantage. They found that using pathological basis of disease as a fulcrum, and critical clinical thinking/reasoning as an anchor, a digitally-enabled generation of medical students embraced this educational tool[3].

Pospisilova, *et al* (Italy) created a teaching environment in a computer-equipped and networked classroom dedicated to histology practical sessions. The e-learning format of histology practical based on virtual slides was found to be an efficient method of teaching histology. Students evaluated positively their use of virtual slides. Teachers benefitted from a uniform quality of slides and also from a straight forward and easy communication method with the students[8].

Syzmas, *et al* (Lithuania) development and evaluation of the user-friendly web based virtual microscopy for teaching dental students basic and oral pathology. Most of the students regarded using virtual slides at their convenience as highly desirable. Faculty considered the use of the virtual microscope for the study of basic as well as oral pathology as a significant improvement over the light microscope[9].

Ordi, *et al* (Spain) determined the impact in student scores when moving from conventional microscopy to virtual microscopy. They also assessed the students' impressions and changes in study habits regarding the impact of this tool. They found that Virtual microscopy can effectively replace the traditional methods of learning pathology, providing both mobility and convenience to medical students[10].

Sagol, *et al* (Turkey) evaluated the use of virtual microscopy in practical pathology sessions and its effects on the students of undergraduate education. The evaluation of the ratings showed that the students were easily adapted to the use of virtual microscopy. They found it user-friendly and thought that the opportunity of viewing slides at home was advantageous. Collaboration between students and interactive discussions was also found to be better improved with this technique[7].

Foad (Saudi Arabia) evaluated the acceptance of the virtual microscopy and its learning outcomes compared with the conventional light microscopy. The students' performances in our study in the virtual microscopy group was better than those of the conventional light microscopy group. The potential advantages of virtual microscopy include active student engagement in sessions, better coverage of learning objectives, and the practicability of self-directed learning[11].

Vainer, *et al* (Denmark) describe how virtual microscopy system for teaching pathology and histology was implemented, from an administrative, an economic, and a teaching perspective. Digital microscopy was received positively by both teachers and students, and a decision was made to convert all courses involving microscopy to the virtual microscopy format, phasing out conventional microscopy[12].

Elmore, *et al* (USA) studied the use of virtual microscopy in training pathology residents. The positive attitudes of pathology trainees toward future use of digital whole slide imaging highlight the importance of exposure to this technology in training programmes[13].

Cho, *et al* (USA) studied the use of digital pathology which has become an integral part of pathology education in recent years, during the COVID-19 pandemic, for its potential utility as a teaching tool. Majority of the trainees showed an improvement in their scores, which demonstrates the utility of Whole slid image-based self-assessment learning as a source of improving diagnostic skills of pathology trainees in a short period of time[14].

Inspite of the many advantages, there are certain challenges and concerns regarding the use of digital images for teaching-learnng. Students may not know

how to use a traditional microscope if virtual microscopy is used extensively[4]. Virtual microscopy replacing the traditional optical ones may result in a pathology resident using a light microscope for the first time, on the first day of their residency[2]. This issue can be addressed by providing glass slides for light microscopy alongside the digital images and encouraging to use the same.

Teacher-student interaction is also a concern. It could be possible that virtual microscopy would decrease the dynamic interaction between teachers and students[1]. However this has not been found in any of the studies[1].

In low resource areas such as in our setting, there are certain technical challenges. Access to the Internet on academic networks is often slow and expensive. Aside from the cost, other technical aspects such as unreliable supply of electrical power and adverse weather conditions which could disrupt telecommunications[1,5].

Limitations : Limitation in this study, were that the performance in the test were not conclusive as the topics were few. Also the students' academic ability varies and the performance is also dependent on the difficulty level of the topics.

The Way Forward is to make available a set of a standardised digital slide collection in the Department, adding related images and case studies. This could also be used for training fresh pathology residents. It could be implementation in other subject curricula. The slides would also be useful when preparing for the postgraduate entrance exams.

At present, the very high cost of the slide scanners is the main reason for slow adoption of digital pathology by medical institutions in countries like India. An alternate therefore would be to capture relevant fields under different magnifications and store them as static digital images (photomicrographs)[5]. Relevant annotations and case studies can be combined. The digital slides can be supplemented with the availability of a small set of glass slides. This method is not as effective as Virtual microscopy,[4] considering the cost of a digital scanner, it is much more cost-effective. Also for examinations, only static digital images can be used[9,12].

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Original Article

Comparative Study on Short Term Outcome Between Laparoscopic Appendectomy and Open Appendectomy in Patients Attending a Rural Tertiary Care Hospital

Sayan Chakrabarty[1], Shib Shankar Kuiri[2], Kanchan Kundu[3], Md Hakim Mia[4]

Abstract

Background : Appendicitis continue to be one of the most common acute abdominal conditions that require immediate surgical treatment. Like other minimal invasive surgeries the laparoscopic approach for treating appendicitis is getting popular nowadays. In cholecystitis, the laparoscopic approach has emerged as the clear gold standard. However, in appendectomy different schools of thought exist regarding the method to be followed.

Aims and Objectives : To compare the short-term outcome between Laparoscopic Appendectomy and Open Appendectomy in patients with acute appendicitis attending Bankura Sammilani Medical College and Hospital.

Materials and Methods : A hospital based prospective comparative study was conducted in the Department of General Surgery BSMCH with a time frame of about one and half years. A total no of 34 patients admitted in the Department of General Surgery with the diagnosis of acute appendicitis and underwent Appendicectomy (Open or Laparoscopic) has been studied.

Result : Seventeen (50%) patient underwent Laparoscopic Appendicectomy. Rest 17 (50%) underwent Open Appendicectomy. There are no statistically significant difference between these two groups in terms of Duration of Operation (P=0.2810). But the Return of bowel function (P=0.0265), Pain score (p=0.008521), Hospital stay (P=0.0092) and Return to work (P=0.0261) significantly in favour of Laparoscopic Appendicectomy.

Summary and Conclusion : Laparoscopic Appendectomy is a safe and effective procedure in the treatment of appendicitis with shorter hospital stays, significantly less postoperative pain, early return of bowel function than Open Appendectomy. As a result, the patient is able to return to work in the earliest opportunity.

Key words : Laparoscopic Appendicectomy, Open Appendicetomy, Bowel Function, Pain Score.

"Forgettable, yet not so forgotten" This underdeveloped residuum of the caecum has no known function and is commonly termed as a "vestigial" organ, yet diseases of the appendix loom large in surgical practice and appendicitis continue to be one of the most common acute abdominal conditions that require immediate surgical treatment[1,2].

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Editor's Comment :

- Unlike laparoscopic cholecystectomy for cholecystitis, laparoscopic appendectomy has not been considered as gold standard treatment for acute appendicitis till date. But due to advantages like less post operative pain, less chance of wound infection, shorter duration of hospital stay and early return to work, over open appendicectomy, laparoscopic appendicectomy needs to be considered as a safe and effective choice for emergency appendicectomy.

Approximately 7-10% of the general population develops acute appendicitis with the maximal incidence being in the second and third decades of life[3].

An appendectomy may be performed as a laparoscopic or as an open operation. Open Appendectomy (OA) has been the gold standard for more than a century as far as surgical removal of the appendix is concerned[4].

Minimal-invasive surgery has rapidly evolved as a major specialty in the past decade[5].

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Recently, several authors proposed that Laparoscopic Appendectomy (LA) should be preferred for the treatment of appendicitis. Advantages of LA such as less pain, faster recovery, fewer wound infections, improved cosmesis, and less postoperative morbidity are obvious from the various randomized trial conducted worldwide comparing OA and LA. A review of the world literature suggests that definitely, the trend is moving from open to LA[6].

Overall morbidity in Appendectomy depends on the severity of appendicitis rather than the operative approach. Even after several independent studies and Meta-analyses the final word has not yet been said. Contrary to Laparoscopic Cholecystectomy, Laparoscopic Appendectomy is still in its nascent state of standardization[7].

Bearing in mind that Laparoscopic Appendectomy unlike other laparoscopic procedures, has not been found superior to open surgery for appendicitis, we designed the present study to determine any possible benefits of the laparoscopic approach[8].

Aims and Objectives

General :

Comparative study on the short-term outcome between Laparoscopic Appendectomy and Open Appendectomy in patients with acute appendicitis attending Bankura Sammilani Medical College and Hospital.

Specific :

To estimate the duration of surgery between two groups

To compare the effectiveness and Postoperative outcome between two groups

To measure the length of stay in hospital between two groups of the patients.

Materials and Methods

Prospective comparative study in the Department of General Surgery, BSMCH, Bankura among all patients undergoing Appendectomy for acute appendicitis after clinical and radiological confirmation. The Study conducted for a period of one and half yrs (March 2021 to August 2022) after Institutional Ethical Committee clearance. Patients have been divided into two groups according to their preference.

Both arms are in control of each other.

Estimated sample size for this study is 34 .

So, 17 cases went for Laparoscopic Appendectomy and another 17 underwent Open Appendectomy for acute appendicitis.

Inclusion Criteria :

Patients with appendicitis are advised for undergoing Appendectomy in the age group of 11-75 years. Patient with equivocal Alvarado score but USG findings are showing NON inflamed appendix and at the same time excluding any other pathology for abdominal pain also included for appendectomy on clinical grounds

Exclusion Criteria:

(1) Patients not willing to give consent.

(2) Patients with pregnancy, shock on admission, known coagulation disorder and history of major lower abdominal operation.

(3) Patients with an appendicular lump, appendicular abscess and generalized peritonitis.

(4) Patients in whom laparoscopy is contraindicated like a severe cardiopulmonary disease.

(5) Patients with Severe co-morbidities like uncontrolled Diabetes, Hypertension and Renal Failure.

Data has been collected via interview, clinical examination, radiological findings and scrutinizing relevant medical records. A pre-designed and pre-tested questionnaire is used for data collection. Informed consent has been sought from each patient before collecting data. Each patient has been followed up after operation. Data has been summarized for estimating various parameters like mean duration of surgery and hospital stay, pain score, requirement of analgesics, post op complications and return to work after surgery etc.

Result and Observation

Thorough observation and analysis of all parameters of the patients included in the study are as follows.

Out of a Total of 34 patients who underwent Appendicectomy 21 were females and 13 were males.

Of 21 Females who underwent Appendectomy, 13 had undergone Laparoscopic Appendicectomy (LA=76%) and 8 had Open Appendicectomy (OA=47.06%).

Of 13 Males who underwent Appendicectomy, 4 had undergone Laparoscopic Appendicectomy (LA=23.53%) and 9 had Open Appendicectomy (OA=52.94%).

The majority of study population was in the age group of 21-30 years, of which Open Appendicectomy was preferred in the age group of 11-20 years (83.33%). In the age group of 21- 30 years, most of the patients opted for Laparoscopic Appendicectomy (69.23%).

In 5 patients Open Appendicectomy was done within 40 mins, while in 1 patient had the procedure of Laparoscopic Appendicectomy done within 40 mins. 12 patients had Open Appendicectomy with operative time around 40-60 mins, whereas 14 patients had the procedure of laparoscopic done within the same duration. Only 2 patients had Laparoscopic Appendicectomy with an operative time of more than 60 mins. Duration of surgery is not significant statistically (p=0.2810) between the two methods (Table 1).

In 9 patients who had Bowel function returned to normal within 6-12 hours and had undergone Laparoscopic Appendicectomy, whereas only 3 patients with Open Appendicectomy had the same. 10 patients had their bowel function back to normal in the Open Appendicectomy group within 12-17 hours whereas 6 patients had their bowel function back to normal in the laparoscopic appendicectomy group within 12-17 hours. Only 2 patients in Laparoscopic Appendicectomy had bowel function return to normal in 18-24 hours and 4 patients in Open Appendicectomy had bowel function return to normal in 18-24 hours.the difference between this two group was statistically significant (P=0.0265).

In 15 patients had Post op VAS pain scoring of 2-3 in the Laparoscopic Appendicectomy group compared to 8 patients in the Open Appendicectomy group. 9 patients had post-op VAS pain scoring of 4-5 in the open Appendicectomy group compared to only 1 patient in the Laparoscopic Appendicectomy group. 1 Patient in Laparoscopic Appendicectomy had a Post-op VAS pain scoring for 5-6.significant P value of 0.008521 (Table 2).

Only 2 patients in the Laparoscopic Group had wound infection compared to 15 patients with no infection. 6 Patients had wound infections in Open Appendicectomy compared to 11 patients with no infection.

14 Patients had a Hospital Stay of 2 Days in Laparoscopic Appendicectomy groups. 5 Patients had a hospital stay of 2 Days in Open Appendicectomy groups. 6 people had Open Appendicectomy with a duration of Hospital Stay of around 3 days whereas 1 patient had a hospital stay of 3 days. 4 Patients had a hospital stay of around 4 Days for an Open Appendicectomy. Only 1 patient with an Open appendicectomy had a hospital stay of 6 days. Duration of hospital stay statistically signicant with a P value of 0.0092 (Table 3).

The majority of the patients were able to return to work postoperatively within 2-3 days (Laparoscopic = 15 and Open = 11). 5 patients in the Open appendicectomy Group had taken more than 6 days to return to work compared to 1 patient in the laparoscopic appendicectomy postoperatively (p value 0.0261)(Table 4).

Table 1 — *Relation between Duration of Surgery and Type of Procedure*

Operative time	Laparoscopic	Open	Grand Total
20-39	5	1	6
40-60	12	14	26
>60		2	2
Grand Total	17	17	34

Table 2 — *Relation Between Post-operative VAS Pain Scoring and Type of Procedure*

Post Op VAS Pain Scoring	Laparoscopic	Open	Grand Total
2-3	15	8	23
4-5	1	9	10
6-7	1		1
Grand Total	17	17	34

Table 3 — *Relation between Length of Hospital Stay and Type of Procedure*

Hospital Stay (Days)	Laparoscopic	Open	Grand Total
2	14	5	19
3	1	6	7
4	1	1	2
5	1	4	5
6		1	1
Grand Total	17	17	34

Table 4 — *Relation between Return to Work and Type of Procedure*

Return to work (Days)	Laparoscopic	Open	Grand Total
2-3	15	11	26
4-5	1	1	2
6-7	1	5	6
Grand Total	17	17	34

Discussion

A total of 34 patients underwent surgery for appendicular pathology between March, 2021 to August, 2022. All patients who underwent LA were included in the study. There were 13 male patients while female patients were 21. Of the 13 male patients, 4 patients underwent LA while 9 patients underwent OA. 13 female patients underwent LA, while 8 female patients underwent OA.

The patient ages ranged from 11-75 years. The majority of the patients who underwent LA were in the age group 21-30 years and it was the same for OA. In a review by Schreider LD; Zimmermann et al. noted the average age for patients undergoing LA was 25.3 years, which compares well with the study[9]. The youngest patient in the study underwent OA. This is comparable to the result obtained in a study carried out by Paya K, Fakhari M, *et al* in which LA was not performed in the pediatric age group due to a more difficult technique, expected risk, and suspected high rate of complication[10]. There were eight patients with appendicitis in the age group >51 years in the study groups.

The duration of operation was Longer in the LA group compared to the OA group but statistically non significant. The median operation time for the LA was 30-60 minutes while that of OA was 20-40 minutes. These findings are similar to those of Long KH; Bannon MP, *et al*[11]. A review by Puser Jochanan G; Greenberg Dan noted/found that operation time was longer in the OA group compared to LA but the difference was not statistically significant[12]. The long operating time could be attributed to the learning curve. Most of the personnel involved, the nurses and other support staff are not trained in laparoscopic surgery and instrument handling.

Return of Bowel function is seen to be earlier in Laparoscopic Surgery around 6-11 hours. There was significant difference statistically (p=0.0265) as by 12-17 hours majority of the patients in both the laparoscopic and open appendectomy groups had their bowel function return back to normal. Only in 6 cases, it was observed that the return of bowel function took 18-24 hours (Lap group = 2 and Open group = 4)[13].

Patients who underwent LA had a shorter hospital stay compared to the OA group with a statistically significant p value of 0.0092. The average duration of hospital stay for the LA group in the study was 3 days while for the OA group was 5 days. When compared with a study by Puser Jochanan G; Greenberg Dan found that the average hospital stay was 2.5 days in the LA group and 2.7 days in the OA group and there was no statistical difference[12].

There were very few complications noted in the study. In the LA group, only 2 patients (5.88%) developed wound infection which was managed conservatively and resolved. For those undergoing OA, the most common is wound sepsis, which occurred, in 17.65% of the patients. These results compare well with the study done by Anderson DG; Edelman DS in that there were minimal complications after LA. Jochanan G; Greenberg Dan[12] in their review noted that there were no significant differences in intra and postoperative complications. The rest of the patients, in LA - 97% and OA - 97.6% had resolution of symptoms.

Most of the patients in the Laparoscopic Appendicectomy and Open Appendicectomy groups were able to return to work in 2-3 days. But in Open Appendicectomy, 5 patients took more than 6 days to return to work due to Postoperative pain compared to 1 patient in the laparoscopic appendicectomy group. The findings are significant (p=0.0261) and synchronous with the findings of the study by Anderson DG; Edelman DS[14].

The pain score in this study was higher in open (10.12±3.9) than in laparoscopic (4.79±4.1) which was due to longer incision stretches of the muscles and wound infection and this was found to be statistically significant at a p-value less than 0.05. Although classic open appendectomy is simple and effective, it has some drawbacks including wound sepsis, delayed recovery and the possibility of unnecessary appendectomies[15]. In this study, Laparoscopy significantly improved the postoperative wound infection rate which is in concordance with the study done by Marzouk M, *et al*[16].

Pain score and duration of Analgesic used were found to be less in the Laparoscopic group ie, (3.2±1.4) & (4.79±4.1) and (4.1±1.8) & (10.12±3.9) in the open group respectively and this difference was found to be statistically significant at $p<0.05$ which is in agreement with another study[17].

Conclusion

We concluded that Laparoscopic Appendectomy is a safe and effective procedure in the treatment of acute

appendicitis. It has shorter hospital stays and significantly less postoperative pain than Open Appendectomy. Laparoscopic Appnedicectomy leads to early return of bowel function, and it also reduces the rate of postoperative wound infection as compared with open appendectomy. As a result, the patient is able to return to work in the earliest opportunity. But the timing of operation in odd hours and the cost-effectiveness of a laparoscopic procedure need to be considered.

Sources of Support : Nil.

Conflict of interest : None.

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Original Article

A Study of the Etiology and Bleeding Manifestations in Patients of Acute Fever with Thrombocytopenia

Sukriti Joshi[1], Prajakta Prakash Patil[2], Supriya Barsode[3]

Abstract

Background : In a tropical country like India, people with acute febrile illness are more likely to have an infectious aetiology and may have associated thrombocytopenia.

Materials and Methods : Over a period of 18 months, 80 patients from 18 to 90 years of age, male and female, with history of fever of acute duration with thrombocytopenia (platelet count less than 1,50,000/mm^3 on admission) admitted in BHRC, Pune were selected by using simple random method. The study was conducted after ethical clearance from the Ethics Committee.

Results : 57(71.25%) were males and maximum patients were in the age group 21 to 30 years (31.2%). Maximum number of patients presented with 1-3 days of history of fever (n=48, 60%). The maximum number of cases suffered from dengue (n=46 57.5%), followed by Malaria (n=16, 20 %) and COVID-19 (n=9, 11.3%). In cases reporting to hospital after more than 5 days of fever (n=4, 5%) had a higher median of platelet count, 78,000/mm^3. The most common physical manifestation of thrombocytopenia was petechiae (8.8%). In 50% of septicaemia cases displayed petechiae. Malaria cases displayed petechiae (18.75%).

Conclusion : As the duration of fever progressed from day 1 to day 6 the Platelet count also showed decreasing trends. Petechiae were the most common manifestation, followed by hematuria, per rectal bleed and epistaxis. The major causes of bleeding manifestations of patients in our study were septicemia and leptospira, followed by Malaria, Dengue and COVID-19.

Key words : Fever, Dengue, Platelets.

Febrile is derived from the word 'febris' which means fever in Latin. Pyrexia is another word for fever, derived from the Greek word 'pyretus' meaning fire.

Fever is considered one of the body's immune mechanisms to neutralize the perceived threat inside the body[1]. Febrile thrombocytopenia, defined as a platelet count less than 1,50,000/mm^3 along with an increase in average body temperature of 98.6 degrees Fahrenheit (37 degrees Celsius), can be associated with many viral, bacterial, autoimmune and idiopathic conditions. The normal platelet count is 1,50,000-4,50,000/mm^3. Platelets are generally derived from the bone marrow from their progenitor cells known as megakaryocytes and have a life span of 10 days. Thrombocytopenia is seen due to diminished production, augmented sequestration or destruction of platelets[1]. There has been a rise in the number of patients with fever and thrombocytopenia recently. Common causes of fever with thrombocytopenia include Dengue, Malaria, Leptospirosis, Chikungunya, Kyasanur Forest Diseases, Scrub Typhus, Miliary Tuberculosis, Typhoid, Human Immunodeficiency Virus (HIV) and recently, Coronavirus Disease-19 (COVID-19). This study demonstrates the correlation between platelet counts and bleeding manifestations to enable us to estimate the correct timing for transfusion of platelets to avoid needless platelet transfusions to such patients.

Editor's Comment :

- It is imperative that we analyze low platelet count as one of the diagnostic marker of common infections and form a systematic approach that is conducted with an awareness of different causes of fever with thrombocytopenia, streamlining the differential diagnosis and specific etiology.
- This study demonstrates the correlation between platelet counts and bleeding manifestations to enable us to estimate the correct timing for transfusion of platelets to avoid needless platelet transfusions to such patients.

Materials and Methods

The study was conducted after ethical clearance from the Ethics Committee at Bharati Vidyapeeth Deemed University Medical College and Hospital, Pune.

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Biochemical and pathological analysis was done in the Department of Biochemistry and Department of Pathology, Bharati Hospital and Research Centre (BHRC), Pune. With adherence to the Helsinki declaration, informed consent in the prescribed format was obtained from all patients included in the study after explanation of the probable benefits in local language. Over a period of 18 months, 80 patients from 18 to 90 years of age, male and female, with history of fever of acute duration with thrombo-cytopenia (platelet count less than 1,50,000/mm^3 on admission) admitted in BHRC, Pune were selected by using simple random method. Exclusion criteria included: patients with febrile thrombocytopenia due to non-infective etiology like immune thrombo-cytopenia, drug-induced thrombocytopenia, hemolysis, elevated liver enzymes and low platelets (HELLP syndrome), myelo-proliferative diseases, disseminated intravascular coagulation of non-infective etiology (abruptio placentae, snake bite), patients with chronic liver disease, and patients with autoimmune disease. One standard questionnaire was used for each patient including personal data, demographic information, detailed history of present illness, drug usage, past disease history and physical examination. Risk factors such as Hypertension, Diabetes Mellitus, coagulopathy and autoimmune diseases were noted. Relevant laboratory investigations were sent including Complete Blood Count (including Total Leucocyte Count, Platelet Count), Renal Function Test, Liver Function Test, PT and INR, and urine routine. Tropical fever workup and other special investigations (including ECG, USG abdomen pelvis, X-ray chest) were done if clinically indicated. Platelet count estimation was done using electrical impedance method in the automated hematology analyzer in the BHRC laboratory. Repeat platelet count was done on day 3, day 5 and then on discharge in patients with platelet count between 40,000/mm^3 - 1,50,000/mm^3.

Random/single donor Platelet transfusion was considered in patients with Platelet count of 10,000/mm^3 as absolute indication with or without bleeding manifestations. Relative indications included Platelet countless than 20,000/mm^3 and presence of bleeding manifestations regardless of platelet count.

Results

The study subjects were in the range of 18 to 78 years. Out of 80 patients, 57 (71.25%) were males and 23 (28.75%) were female. Maximum patients were in the age group 21 to 30 years (31.2%).

Maximum number of patients presented with 1-3 days of history of fever (n=48, 60%), followed by history of fever since 4-5 days (n=28, 35%) and history of fever since more than 5 days (n=4, 5%).

The minimum Platelet count was 10,000/mm^3. Maximum was 1,49,000/mm^3. The cases who reported within 1 to 3 days of the start of fever (n=48, 60%) were more likely to present with a higher platelet count (median = 49,500/$mm^{3)}$. The cases who reported to hospital within 4 to 5 days of onset of fever (n=28, 35%) had a lower overall platelet count with a median of 47,500/mm^3. In cases reporting to hospital after more than 5 days of fever (n=4, 5%) had a higher median of platelet count, 78,000/mm^3; however, the frequency of cases below the median was higher.

The maximum number of cases suffered from Dengue (n=46 57.5%), followed by Malaria (n=16, 20%) and COVID-19 (n=9, 11.3%). Swine flu and viral fever had the minimum number of cases (n=1, 1.3 % each).

Patients suffering from septicaemia had the highest incidence headache with 100% patients complaining of headache. Further, patients suffering from COVID-19 had maximum incidence of symptoms of arthralgia/myalgia- 66.67% and headache- 88.89%, while dengue patients suffered from the same at 45.65% and 65.22%, respectively.

Nausea and vomiting seen most frequently in viral fever, enteric fever and leptospirosis (100% in all), followed by Dengue 67.39% and Malaria 62.5%.

Altered sensorium was seen in 22.22% of COVID-19 patients.

Out of the subjects studied, majority of the patients did not have any active bleeding manifestations (76.3%) despite having thrombocytopenia. The most common physical manifestation of thrombocytopenia was petechiae (8.8%). 50% of Septicaemia cases displayed petechiae. Malaria cases displayed petechiae (18.75%), followed by menorrhagia and bleeding per rectum (PR) (6.25% each). Dengue cases showed a wide variety of bleeding manifestations with 6.52% demonstrating petechiae followed by epistaxis (4.35%) and hematuria (4.35%). In 11.11% of COVID-19 positive patients showed ecchymotic patches. None of the cases with enteric fever, swine flu or viral fever showed any bleeding manifestations.

Discussion

In our study, a majority of patients belonged to the

age group of 21-30 years, followed by 31-40 years. A similar study by Gondhali et al also reported the maximum cases in the age group of 21-30 years[2]. In the present study, the male to female ratio was 2.5:1. As in our study, several other studies on febrile thrombocytopenia have reported male preponderance, including Choudhary, *et al*, Radhika, *et al*, Sumangala et al and Naikwadi, *et al*[3-6].

Maximum number of patients presented with 3 days of history of fever (31.25%), followed by history of fever since 2 days (22.5%), followed by 20% of patients who had history of fever since 4 days.

A study by Fah, *et al* reported that patients presented with fever ranging from 2-10 days[7]. Kandagatla, *et al* reported that all patients showed unspecified fever, with the duration varying from 1-5 days to >15 days, while most of them exhibited fever in first 5 days (65%)[8].

In our study, the median platelet count on day 1 of admission was 49,000/mm^3, with the minimum being 10,000/mm^3 and maximum being 1,49,000/mm^3. Nair et al displayed a platelet count range of >50,000/mm^3 in 83 (46.11%) patients, 20000-50000/mm^3 in 43 (23.89%) and <20,000/mm^3 in 54 (30%) of patients. Radhika, *et al* displayed platelet count <20,000/mm^3 in 35 (4%) cases. Naikwadi, *et al* demonstrated <50,000/mm^3 in 18 (18%) patients[4,6,9].

In our study, classifying the Platelet count further based on the duration of fever at the time of hospital admission, 60% of patients who had duration of fever of 1-3 days at the time of admission to hospital had a median platelet count of 49,500/mm^3. Jayanthi, *et al* studied the correlation between Platelet count and other parameters to the duration of hospital stay in dengue fever with thrombocytopenia. They found that there was a significant negative correlation between platelet count and duration of hospital stay, which could be explained as number of complications increasing as the platelet count decreased[10].

The first three causes of febrile thrombocytopenia in our study are Dengue (57.50%), Malaria (20%) and COVID-19 (11.25%), followed by Enteric fever (3.75%), Leptospira and Septicemia (2.5% each) and Swine flu and Viral fever (1.25%). Lohitashwa, *et al* had similar findings for Dengue and Nair, *et al* showed similar numbers for Septicemia[11,9]. Bhalara, *et al* found the causes of febrile thrombocytopenia in their study to be Dengue (28.6%), Malaria (22.8%) and septicaemia (6.3%)[12]. Sumangala, *et al* found the causes to be Dengue (53%), Malaria (15.6%) and septicaemia (8.7%)[5].

As Dengue fever was the major etiological disease in our case study, we studied it in detail. The median Platelet count was found to be 45,000/mm^3, with 50% patients having a Platelet count between 25,000 and 86,000/mm^3. Nelson, *et al* reported that 85% patients with Dengue had a thrombocytopenia with a Platelet count below 1,05,000/mm^3.[13]

Malaria was the second most common etiology for thrombocytopenia in our study (20%). Malaria patients usually developed thrombocytopenia around 3-5 days of fever. according to presence of thrombocytopenia was not a distinguishing feature between the two types of malaria Jadhav, *et al*[14].

In a study on over two thousand patients with fever, Erhart, *et al* reported platelet count of less than 1,50,000/mm^3 increases the likelihood of Malaria by 12-15 times. Various other studies have also found thrombocytopenia to be commonly associated with malaria, which resolves after therapy[15].

In both COVID-19 and Dengue infection, patients can present with overlapping clinical features such as fever and myalgia as well as thrombocytopenia.

In our study, of all the patients presenting to the hospital with 3, 4 or 5 days of fever, the most common aetiology was dengue, followed by malaria and COVID-19.

In our study, arthralgia and myalgia were found in 42.5% of cases. Fah, *et al* reported arthralgia/myalgia and nausea/ vomiting in 69.7% cases in their study[7].

In our study, headache was also reported by 66.25% cases of all aetiologies except swine flu and viral fever. Gajbhare, *et al* reported headache in 44% of cases in their study, while Kandagatla, *et al* reported headache in 30.63% cases[16,8].

In our study, altered sensorium was reported by 5% of cases. In a study by Gondhali, *et al* altered sensorium was reported in 15% of cases[3].

In our study, 25% cases presented with bleeding manifestations. Petechiae (8.75%) was the major presentation, followed by hematuria (3.75%) and epistaxis, menorrhagia and PR bleed (2.5 % each) in our study. Lohitashwa, *et al* had bleeding manifestations in 49% of patients with 63% showing petechiae. Nair, *et al* had 41% bleeding with 22.22% petechiae.

In our study, 44% patients with severe thrombocytopenia (platelet count between 20,000- 50,000/mm^3) experienced bleeding manifestations, while only 3.7% patients with moderate thrombocytopenia had bleeding manifestation .

Similar to our study, several studies including Harsha, *et al*; Kashiv, *et al* and Gondhali, *et al* have reported that bleeding manifestations were more frequent when the platelet counts were <20,000/mm^3.[17,18, 2]

In our study, ecchymosis was the only bleeding manifestation observed in COVID-19 patients (11.1%). A maximum variety of bleeding manifestation was observed in dengue patients, with 6.52% reporting petechiae, 4.35% reporting epistaxis and hematuria, followed by 2.17% of patients reporting hematemesis, malena, menorrhagia and per rectal bleed. In malaria patients, petechiae were reported by 18.75% patients followed by menorrhagia and per rectal bleed which was reported by 6.25% patients each, in our study.

In comparison, in a study by Nelson et al on dengue patients, 72% had hemorrhagic skin manifestations, most often a subtle petechiae eruption on the extremities. Epistaxis was found in 17%; gastro-intestinal hemorrhage 11%, 45% had menstrual irregularities, 17% had no hemorrhagic findings[13].

Gondhali, *et al* reported that 6 (10.71%) out of 56 patients had bleeding[2].

Study Limitations : The COVID-19 pandemic broke out after this study was initiated. Hence recruitment of subjects in the study was delayed and was not a true representation of cases of the pre- COVID-19 era. Our study sample was small and also included only a single centre and hence the adequate representation of the entire population cannot be made.

Conclusion

Maximum patients of fever with thrombocytopenia were in the age group of 21-30 years. The male: female ratio was 2.5:1. Duration of fever at the time of admission had significant correlation with thrombocytopenia. As the duration of fever progressed the platelet count also showed decreasing trends. The most common etiology of thrombocytopenia in our study was Dengue, followed by Malaria and COVID-19. Petechiae were the most common manifestation, followed by hematuria, per rectal bleed and epistaxis.The major causes of bleeding manifestations of patients in our study were Septicemia and Leptospira, followed by Malaria, Dengue and COVID-19.

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Conflict of Interest : None

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Original Article

Hematological Parameters as Morbidity and Mortality Predictors of Sepsis

Taranpreet Kaur[1], Amit Varma[2], Rohit[3], Kirandeep Kour[4]

Abstract

Background : Diagnosing and treating Sepsis is a challenging situation. It becomes imperative to know about the factors that can deteriorate the situation further. Although there are biomarkers available for diagnosis and prognostication of Sepsis, yet they are time consuming and not readily available in resource limited settings. This study aims to find the role of Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR) as predictor of outcome in sepsis.

Material and Methods : This was an observational, prospective study where a total of 115 patients diagnosed with Sepsis by qSOFA >2 on admission or change in SOFA score >2 from baseline were included. The aim of study was to look for the role of Neutrophil Lymphocyte Ratio, Monocyte Lymphocyte Ratio and Platelet Lymphocyte Ratio as morbidity and mortality indicator in patients with sepsis.

Results : Platelet Lymphocyte Ratio (PLR) and Neutrophil Lymphocyte Ratio (NLR) were found to have maximum predictability of mortality (99.1%). Similarly, NLR and PLR were also found to be statistically significantly higher in those requiring Mechanical ventilation and Renal replacement therapy.

Conclusions : Both Neutrophil Lymphocyte Ratio and Platelet lymphocyte Ratio have been found to have positive correlation with the poor prognosis in case of Sepsis. They can be quite useful in the resource limited settings.

Key words : Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), All cause mortality, Vasopressors, Renal Replacement Therapy, Mechanical Ventilation.

The origin of the word "*Sepsis*" dates back to around 2700 years ago. Derived from greek word 'Sepsin'[1] which means "*To make putrid*".

Sepsis is defined as the body's dysregulated response to the presence of infection resulting in life threatening organ dysfunction[2]. Sepsis is clinically identified by an acute change in the SOFA score by more than 2 points in a patient with suspected bacterial infection[3].

Septic shock is defined as the condition where underlying circulatory, cellular and metabolic process in sepsis are profound enough to increase mortality[2]. Septic shock according to the Sepsis 3 criteria is defined as the need for vasopressors in a patient with sepsis to maintain MAP $\geq$ 65 mmhg or Lactate $\geq$2 mmol/L despite adequate fluid resuscitation[3].

Sepsis is often quite challenging to treat as well as to be diagnosed. Numerous clinical criteria for diagnosis of sepsis have come up over a period of time. It has evolved from Systemic Inflammatory Response Syndrome (SIRS) to q SOFA, (Sequential Organ Failure Assesment) SOFA, NEWS (National Early Warning Score), MEWS (Modified Early Warning Score) and APACHE. These scores can often be used to predict mortality and also provide therapeutic guidance. Apart from these clinical scores there are various Biomarkers also available for diagnosing sepsis, prognostication as well as to predict the response to antibiotics[4]. CRP and Procalcitonin are the ones most frequently used. CRP can be raised in both inflammatory and noninflammatory diseases. Procalcitonin, although a useful marker but is quite expensive and not readily available in the resource limited settings. In 2001, there was another marker recommended as an infection biomarker ie, Neutrophil Lymphocyte Ratio (NLR)[5]. Since then there has been a surge in investigating the role of other simple parameters derived from Complete Blood

Editor's Comment :

- Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) are simple, cost-effective biomarkers that strongly correlate with morbidity and mortality in sepsis.
- Elevated NLR and PLR values can assist clinicians in early risk stratification and prognostication, especially in resource-limited settings

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Count (CBC) which include besides NLR, Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR) and Platelet count to mean platelet volume in various diseases in assessing the disease severity and association with mortality[6-10]. As these markers NLR, MLR and PLR are easy to obtain, cost effective, easily available in the resource limited settings , so this study aims to find the role of NLR, MLR and PLR as prognostic markers and also to find their correlation with CRP, Procalcitonin and Lactate.

Aims & Objectives

(1) To evaluate the role of Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR) as indicator of morbidity and mortality in patients with Sepsis.

(2) Correlation of NLR, MLR and PLR with the already existing markers of sepsis like C Reactive Protein, Procalcitonin and Lactate.

Material and Methods

Study Design :

This was an Observational, Prospective study conducted in a Tertiary Care Center in Dehradun.

Study Setting :

Consecutive patients were enrolled for the study for a period of 1 year after clearance from Institutional Ethical Committee.

Inclusion Criteria :

Patients aged >18 years with underlying infection and Sepsis diagnosed by q SOFA>2 at admission and change in SOFA score >2 from the baseline were included in the study.

qSOFA :

(1) Respiratory rate >22 breaths/min. (2) Altered mental status. (3) SBP<100mm hg

Exclusion Criteria :

Pregnant patients, Immunocompromised patients including HIV,

Those on Immunosupressants. Surgical patients with sepsis,

Those who died within 12 hours of hospitalisation. Those with underlying malignancies were excluded from the study.

Before enrolment, all patients (or their relatives if patient was in altered sensorium) were informed about the study and informed consent was taken.

Detailed history and physical examination was done of all those patients who were then enrolled in the study after screening for Inclusion and exclusion criteria. Patient's sensorium was evaluated by Glasgow Coma Scale which included Eye(E), Verbal (V) and Motor (M) response. Venous samples were then drawn and sent for Haematology, Biochemistry, Arterial Blood Gas Analysis, CRP and Procalcitonin. Paired samples were sent for Blood Culture/Sensitivity (both aerobic and anaerobic) and from other presumed sources of infection before initiating antibiotics. Chest X-ray and Ultrasonography Abdomen were done at the time of admission.

Other investigations like sputum examination, Pleural fluid, ascitic fluid or CSF analysis were also done in selected cases.

Patients were further categorized on the basis of source of infection like Sepsis (Genitourinary cause), Sepsis (Pulmonary cause), Sepsis (Abdominal cause) and Sepsis (Skin and Soft Tissue Infection cause).

Outcomes :

Primary Outcome :

To find the predictability of all cause hospital mortality in patients with altered Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR).

Secondary Outcomes :

To find the correlation of altered NLR, MLR and PLR with ICU stay and total duration of stay in hospital.

Statistical Analysis :

The data collected for the study included :

(1) General information : Name, age and sex of the patient, co-morbidities.

(2) Behavioural traits : Status of smoking and alcoholism.

(3) Laboratory parameters : Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), Total Leucocyte Count (TLC), Procalcitonin, CRP, Creatinine, Bilirubin, Lactate, SGOT, SGPT levels, blood culture, urine culture, Sputum Culture, Pus culture, Ascitic fluid culture, Pleural fluid culture.

(4) Clinical parameters : Glasgow Coma Scale (GCS), Heart Rate (HR), Mean Arterial Pressure (MAP), Respiratory Rate (RR).

(5) Hospitalization parameters : ICU stay, Total duration of stay.

(6) Diagnostic parameters : Source of infection, Tentative diagnosis.

(7) Other parameters : Status of administration of vasopressors, mechanical ventilation and Renal replacement therapy.

The collected data was analyzed in SPSSv28 software

Descriptive analysis was done for different parameters followed by Analysis of Variance (ANOVA) to determine the association of various clinical and other parameters on NLR, MLR and PLR. Correlation analysis was also performed to find out the correlation between NLR, MLR and PLR and different laboratory and hospitalization parameters. Predictability of sepsis outcome based on various parameters like NLR, MLR, PLR and their combinations was deduced using logistic regression and ROC curves were obtained for the most important parameters.

Results

A total of 156 patients were included in the study and subsequently 41 patients were excluded. Finally, 115 patients met the criteria for the study. Diagrammatic algorithm of the study population is shown in Fig 1.

Out of 115 patients, 75 patients survived and 40 patients expired. Various sources of infection in the study population were: Respiratory causes in 59 patients (51.3%), Genitourinary causes in 23 patients (20%), Abdominal causes in 17 patients (14.7%) and Skin and soft tissue infection in 16 patients (14%).

Maximum patients were found to have Pneumonia (54 patients, 46.9%) as cause of infection.

The mean age of the study population was 54.03±0.89 years with range of 27-70 years. There were 64.35% males and 35.65% females in the study population.

In the study population, the survived group and expired group were found to have various comorbidities. Diseases like T2DM, CAD, Hypertension and CKD were found to be higher in the Expired group; whereas diseases like T1DM, CLD, Bronchial asthma, COPD and TB were found only in the survived group.

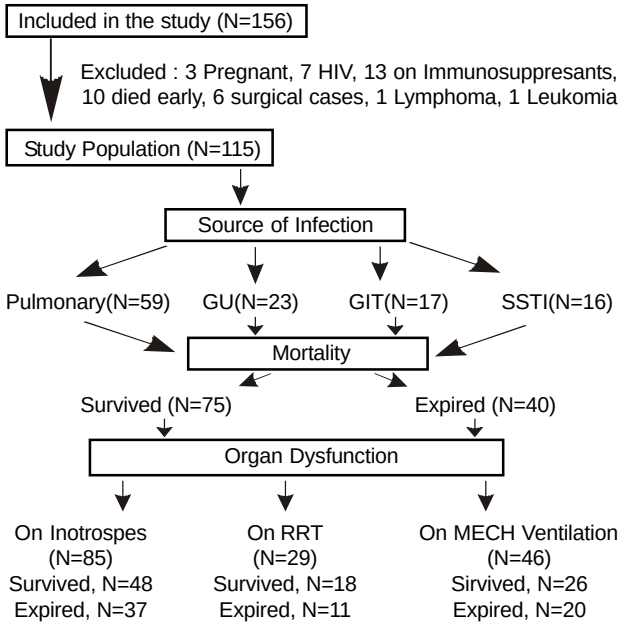

Fig 1 — Diagrammmatic Algorithm of the study population

It was found that the expired group had significantly higher mean Age, SOFA score, significantly lower sensorium as indicated by Glasgow Coma Scale (GCS) compared to the Survived group. Also, vitals like Heart Rate and Respiratory rate were significantly higher in the expired group, Mean Arterial Pressure was significantly lower in the expired group compared to the survived group. Other parameters like number of days in ICU and total duration of stay in the hospital were significantly lower in the expired group.

Also, the Laboratory parameters like Total Leucocyte Count (TLC), Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) had statistically significant higher values in the expired group than the survived group. Other investigations like Lactate levels, CRP, Procalcitonin, Creatinine and Bilirubin too had significantly higher mean in the expired group compared to the survivors (Table 1).

The primary outcome of the study, ie, predicting the all-cause mortality from the altered NLR, MLR and PLR individually as well as in combination, was calculated from the Chi-square test. We found that NLR and PLR in combination were having the maximum predictability (99.10%) of mortality due to sepsis followed by PLR and MLR in combination (97.4%).

Individually, PLR has the maximum predictability of 93.0% followed by NLR which has predictability of

Table 1 — *Effect of baseline parameters on the mortality*

Parameters	Study Population (N=115)	Survived (N=75) Mean±SE	Expired (N=40) Mean±SE
Age (in years)	54.03±0.89	52.05±1.02	58.38±1.39**
CRP(mg/dl)	74.85±1.79	64.29±1.52	94.13±2.07**
Procalcitonin(ng/ml)	9.54±0.22	8.31±0.19	11.89±0.25**
TLC (cells/cu.mm)	24204.43±690.1	20768.51±664.5	30691.00±903.8**
NLR	23.95±0.71	20.14±0.65	31.02±0.89**
MLR	0.72±0.02	0.69±1.55	0.89±1.11
PLR	265.59±7.47	213.76±4.59	359.35±6.24**
Lactate (mmol/L)	3.35±0.09	2.79±0.07	4.38±0.09**
Bilirubin (mg/dl)	1.72±0.09	1.71±0.15	2.00±0.21**
Creatinine(mg/dl)	2.37± 0.11	2.16±0.19	4.22±0.25**
GCS	9.97±0.17	11.18±0.09	7.73±0.12**
HR (beats/min)	135.09±0.84	129.49±0.56	145.30±0.77**
MAP (mm hg)	49.93±0.52	53.08±0.42	44.03±0.57**
RR (breaths/ min)	34.17±0.51	32.07±0.54	38.08±0.74**
ICU Stay (in days)	4.95±0.18	5.43±0.20	3.95±0.28**
Total Stay (in days)	7.55±0.35	9.19±0.32	4.45±0.44**
SOFA score	11±2	9±2	13±2**

** indicates p value ≤0.01

86.10%. Individually, MLR has the least predictability of mortality (68.70%). The AUC for NLR was 0.916 and that for PLR was 0.998 with p value of <0.001.

Secondary outcome of the study was to find the correlation of total duration of stay in hospital and duration of stay in ICU with the altered NLR, MLR and PLR. It was found that all the three parameters ie, NLR, MLR and PLR were found to be negatively correlated with the Duration of stay in ICU and total duration of stay in hospital and the difference was highly significant (Table 2).

The highest correlation was found for PLR with total duration (r=-0.688) and days in ICU (r=-0.488) followed by NLR with total duration (r=-0.534) and Days in ICU (r=-0.349).

Discussion

Sepsis still continues to be among the top 10 causes of mortality. In our study, 40 out of 115 patients ie, 34.78% patients died similar to the study by Kaushik R, *et al* who also found mortality of 33.9%[11]. One of the major cause of high mortality in Sepsis is because of delay in diagnosis and delayed initiation of treatment.

Table 2 — *Correlation of ICU stay and total duration of stay with NLR, MLR and PLR*

Parameters	ICU Stay	Total Stay
NLR	r = -0.349, p<0.001	r = -0.534, p<0.001
MLR	r = -0.296, p<0.001	r = -0.297, p<0.001
PLR	r = -0.488, p<0.001	r = -0.688, p<0.001

The major cause of Sepsis in the study population was found to be Pneumonia followed by Complicated UTI or Pyelonephritis. This is in consensus with the other similar studies done on Sepsis where Pneumonia is the topmost cause of Sepsis in hospitalised patients followed by Genitourinary infections[12-14].

Primary outcome ie, to find the predictability of all cause mortality from altered NLR, MLR and PLR showed that PLR and NLR in combination had the maximum predictability and individually, PLR was found to have maximum predictability of mortality followed by NLR. Spoto S, *et al* also found NLR and PLR to have a high positive predictive value of 96% for mortality in Sepsis[15]. Shen Y, *et al* also found that high PLR at admission was associated with the mortality in patients with Sepsis[16]. Huang Z, *et al* did a meta analysis of 14 studies to assess the role of NLR as a prognostic marker in patients of sepsis. They found that higher values of NLR were found in the non survivors compared to the survivors and hence concluded that NLR has a prognostic role in patients with Sepsis[17].

This is a commonly recognized fact that Sepsis is because of the immune dysregulation and it includes the role of both pro inflammatory and anti inflammatory markers[18]. The increase in NLR in Sepsis can be attributed to the increase in the neutrophils and apoptosis of lymphocytes in Sepsis and also due to some endogenous mediators like catecholamines and cortisol[19,20]. Platelets have a role as an immuno-modulatory agent by causing release of various cytokines and also by interacting with bacteria and various other inflammatory cells, hence resulting in the upregulation of the inflammatory process[21-24].

We also found the AUC of NLR in predicting mortality of 0.916 and AUC of PLR in mortality was 0.996. This is in contrast to the finding of Spoto S, *et al* who found AUC of NLR in predicting mortality as 0.661. However, they took only patients outside the ICU setting and also, they measured 90 day mortality, whereas in our study, only mortality during hospital stay was measured[15]. Findings similar to our study were also reported by Kaushik R, *et al* who found a significantly high AUC of NLR as 0.911 in the early phase of sepsis as compared to the control population[11].

We also found an inverse correlation of NLR and PLR with the total duration of stay in hospital and days in ICU which can be explained by the fact that the patients in the expired group had high NLR and PLR and at the same time, lesser days of stay compared to the survived group. There have been studies in literature where a positive correlation of NLR, MLR and PLR was found with duration of stay in hospital but they were mostly done on diseases other than sepsis where immediate mortality is not comparatively high[25-28].

Other parameters like the need for Inotropes, need for Invasive mechanical ventilation and the need for RRT were found to have a strong correlation with NLR, MLR and PLR. Sari, *et al* also found Invasive mechanical ventilation use among those with high NLR and also who died within the first 5 days of admission[14].

CRP and Procalcitonin are the biomarkers that have been studied extensively in the sepsis followed by other biomarkers like IL 6, Presepsin and CD 64[4]. These markers have role not just for diagnostic purpose but also for prognostication and therapeutic decisions.

Gurol G, *et al* evaluated the CRP, Procalcitonin, WBC and NLR in patients with sepsis and they found that NLR had the best predictive value among all. They also found that CRP and Procalcitonin showed a correlation with NLR[29]. This is in concordance with our study where both NLR and PLR were found to have a strong positive correlation with CRP, Procalcitonin and Lactate.

Conclusion

Hence, we would like to conclude that NLR and PLR have a role as predictor of mortality and morbidity in patients of Sepsis. Higher values of NLR and PLR are associated with the poor outcomes. But, further follow up studies need to be done to see their role in guiding therapeutic decisions.

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Conflict of Interest : None.

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Original Article

Application of Freshly Collected Amniotic Membrane & Amniotic Fluid Dressing on Chronic Non Healing Ulcers Patients — A Hospital Based Experience from Kolkata

Nirmal Polle[1], Niranjan Bhattacharya[2], Pallabi Polle[3]

Abstract

Background : The management of Chronic non healing ulcers possess great challenges because of the high prevalence, refractory nature, high rate of amputation, disfigurement, loss of wages & economic burden[1]. The placenta which was discarded in pits or incinerated so called trash is converted to gold here. Use of freshly collected & screened amniotic fluid and amniotic membrane as biological dressing in treatment of chronic non healing ulcer (the ulcer which doesn't heal completely within 3 months) is potentially beneficial & free of cost.

Material and Methods : Application of autologus skin graft, Aqua cell Ag+ (Silver) dressing, Hyperbaric oxygen therapy, Bioengineered skin, Negative pressure wound therapy, Amnio-Patch, Chorionic mesenchyme, Epi cell cultured Epidermis, Micronised dried Amniotic membrane, Amnion Cytokine extract, 3D Scaffold fabricated with other materials, Decellularised Amniotic membrane are very costly.

Conclusion : Most of these commercial products doesn't have any viable or no cells at all[2].

Key words : Amniotic fluid, Amniotic membrane, Biological Dressing, Non-healing ulcer.

Indian Studies on the epidemiology of chronic wounds estimated the prevalence at 4.5 per 1000 population.

Diabetic foot ulcers occur in up to 15% of all diabetic patients and are a leading cause of non-traumatic amputation worldwide.

The prevalence of vascular ulcer in the US is estimated at 5,00,000 to 6,00,000 and increased with age[3,4].

Focus of Study :

To understand and reveal benefit and potentiality of term intact freshly collected amniotic fluid and amniotic membrane to treat chronic and non healing ulcers in human patients.

Most Important Features of Freshly Collected Amniotic Fluid (AF) & Amniotic Membrane (AM) :

The Amniotic membrane is composed of 2 layers, an epithelial layer, containing 2 epithelial cell types of cuboid or columnar shape capped Amniotic Epithelial Cells (AECs) and a stromal matrix, avascularised layer containing amniotic mesenchymal stromal cells.

Amniotic membrane induces signalling pathways that are involved in cell migration and proliferation. Amniotic membrane contains Platelet Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), Insulin Like Growth Factor IGF), Epidermal Growth Factor (EGF), Basic Fibroblast GF, Transforming Growth Factor (TGF) alpha and beta, Keratinocyte Growth Factor (KGF), Hepatocyte Growth Factor (HGF) & Nerve GF. They have been identified in freshly collected amniotic tissue. Amniotic membrane has antibacterial property mediated by human betadefensins (HB D1-3) and elafin and Secretory Leukocyte Protease Inhibitor (SLPI) & LL37[5], a cathelicidin family, has anti-biofilm properties-combating chronic infections.

Editor's Comment :

- Now we live in Stem Cell age. This novel cell therapy by freshly collected amniotic fluid and amniotic membrane will benefit mankind at large in future both autologous and allogenic, in different areas of tissue repair & in wound healing, in repair of nerves, heart lesions, muscles, organ damage and skin lesions.
- It is potentially beneficial and free of cost.

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Human Amniotic Mesenchymal Stromal Cell (hAMSc) expresses low levels of classical MHC-I molecules found in and do not express MHC-II molecules on their surface, making them suitable for regenerative medicine.

Amniotic fluid rich in :

Amniotic Fluid contain quite a good population of progenitor and stem cells with high telomere content which have unique property to trans differentiate into different lineages and participate in the process of tissue regeneration depending on the provided niche to them[6].

Amniotic Fluid rich in nutrients, growth factors, hyaluronic acid, mesenchymal stem cells essential for non-healing ulcers and wounds[7].

Amniotic Fluids have antibacterial properties also by lysozyme, 7S immunolobulin and lgA.

It has been reported by[8] that only 2 ml AF can provide upto 20,000 cells of which 80% has been stated to be viable.

These cells proliferate rapidly with doubling time 30-36 hours and do not require supportive feeder layers[9].

Pluripotency of AF derived stem cells have been reported by[10] as first evidence. These distinct subpopulations of proliferating cells (0.1-0.5%) expresses pluripotent markers Oct 4 (Octamer binding transcription factor 4).

Combined effect of Freshly collected AF and AM :

The beneficial effects of mesenchymal stem cells of AM & AF, on wound healing through paracrine interactions[11], secrets soluble factors to exert immune modulation, promote angiogensis, decrease wound inflammation, wound ECM remodelling (various components such as fibronectin, collagen and vitronectin provide structural support for the invading capillaries), MSC secret cytokine to promote dermal fibroblast proliferation, antiapoptotic and enhance regeneration of proper skin structure and function.

AM and AF have been used as sources of mesenchymal stem cells for transplantation. Both lineages show adipogenic, osteogenic and chondrogenic differentiation in vitro. They have been applied extensively as a wound dressing, cutaneous and corneal wound healing, as vectors for delivery of genes[12] in nerve regeneration[13] among many others.

Materials and Methods

Study Technique:

(1) Informed consent from patients to treat non healing wound were obtained, including the donor mothers for collecting the amniotic fluid and the amniotic membrane.

(2) Wound was first thoroughly irrigated with normal saline to remove debris, foreign particles, and other contaminants.

(3) Simple wound debridement, done as per demand of that particular ulcer. Again the ulcer is thoroughly washed with normal saline.

(4) Amniotic fluid is applied over wound & around the wound injected subcutaneously.

(5) Amniotic side is applied in superficial ulcers where epithelialisation is needed; chorionic side is applied where vascularisation is needed; amniotic or chorionic membrane is cut as per wound size and shape and wound bed is covered up to skin margin. Plain Vaseline tulle applied over amniotic membrane, then sterile gauzes are applied over it and bandaged with sterile bandage.

(6) Follow up is scheduled on 8th, Day.

Eligible mother was counselled before and informed consent obtained from her for donation of amniotic fluid & placenta.

Recipients were taken informed consent and were screened for HIV-I & II. Hepatitis “B” & “C”, Venereal Disease Research Laboratory Test (VDRL), toxoplasmosis, herpes infection.

Clinical History was taken meticulously.

Types of wounds, size, depth, pain score, exudation were evaluated.

Investigations : Previous investigations were noted and written.

***Recent investigations* —** Complete Blood Count (CBC), C-reactive Protein (CRP), Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), TFT, KFT, LFT, Lipid Profile, HbA1C (if requires) CXR, Electro Cardio Gram (ECG), Echocardiography, USG whole abdomen, Doppler Study (if requires). CT/MRI Scan / HP studies with MVD count, Examination of Pus from wound swab were sent for culture and sensitivity.

Ankle Brachial Pressure index ABPI $\geq$ 0.8 will be included[14].

Co-morbidities any & their evaluation and treatment of underline causes .

Micro Vessel Density Count – Quantitative assay :

Angiogenesis is one of the important pillar of tissue healing apart from Extra Cellular Matrix (ECM) remodelling & re-epithelialization.

Biopsy sample were taken for histopathology study to assess the rate of granulation tissue formation that predicts the quantitative assay of capillary remodelling / angiogenesis by micro vessel density count.

Microvessel Density Count (Fig 1) :

Patient : AM 46 years, Male.

Diabetic Leg Ulcer – healed within 12 weeks (Fig 2).

Patient : MM , Age 55 years, Female , Diabetic Foot Ulcer healed within 12 weeks (Fig 3).

Pictorial presentation of MVD count

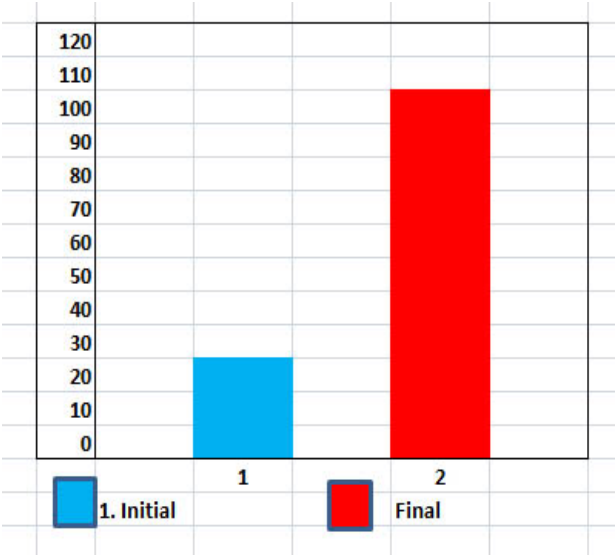


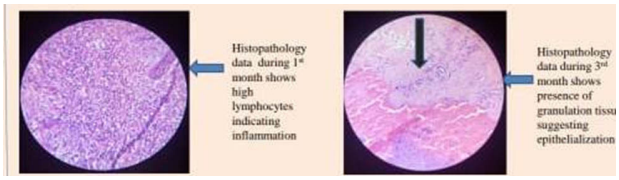
Fig 1 — Histogram showing the mean MVD count comparing histopathology of the junctional biopsy tissue counter stained with Hematoxylin –Eosin at initial and final phase of the study. Results obtained from counts of five randomly selected sites on the slide

Analysis and Results

Application of amniotic fluid and Amniotic Membrane are potential safety and effacious on non-healing ulcers has seen quick epithelialisation and decrease or absence of exudation in 95% of cases. Upon the course of treatment pain score dropped from 80% to 6%. Inflammation decreased to a great extent which was reflected by returning CRP count in its normal range in cases near to complete healing. Wound size decreased gradually and no uneventful circumstance are noted. Tapering of insulin dose and oral anti diabetic therapies were successful. At the end of the 12 weeks number of patients healed 92.59%.

In few cases hypo-pigmentation noted, which gradually returned to normal skin colour within six months follow-up.

Histopathological data –reduction in polymorpho-nuclear infiltration near to healing stage and presence of granualation tissue and new vessels.



Statistical Evaluation :

In this observational and prospective study, 27 patients were included with chronic non healing ulcers with different aetiology. In the control group patients were 21. AM & AF were applied every 8th day.

Friedman's ANOVA with multiple comparisons shows statistically significant ($p<0.001$). At the end of 12th week number of patient healed 25 ie, 92.59% and number of patient not healed 2 ie, 7.41%.

As per our study AM & AF dressing effective not only for reduction of ulcer dimension but also effective in respect to final outcome & healing.

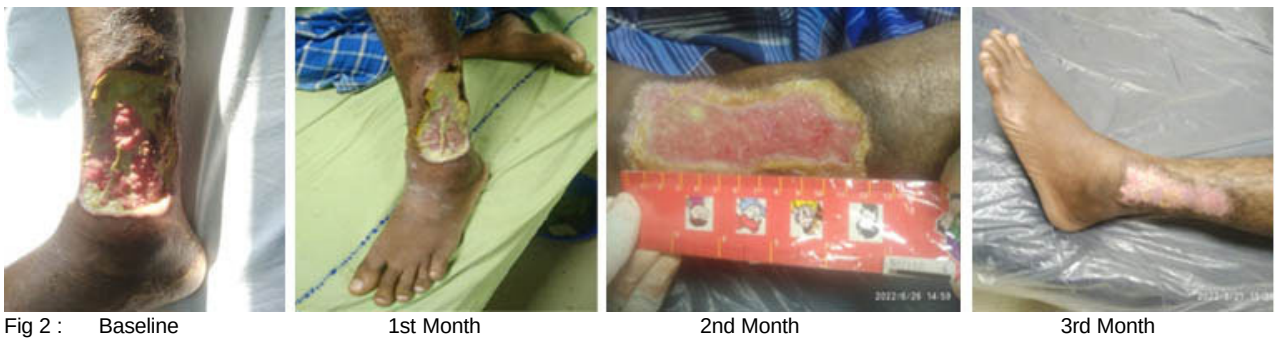


Fig 2 : Baseline 1st Month 2nd Month 3rd Month

Fig 3 : Baseline 1st Month 2nd Month 3rd Month

Conclusion

Freshly collected Amniotic fluid and Amniotic Membrane contains angiogenic[15,16] and pro-apoptotic factors and greatly promotes epithelialisation as it facilitates epithelial cell migration, reinforcement of basal cellular adhesion and encouragement of epithelial differentiation. Apart from that freshly collected Amniotic Membrane bathed in amniotic fluid also showed antimicrobial properties[17], due to presence of lysozyme, lactoferin, hyaluronic acid, cystacin-C, transforming GF beta 3, peroxidases, immunoglobulin and zinc peptide.

The human amniotic fluid contains amniocytes which are a large pool of self renewal cells, mainly fetal in nature. These amniocytes have an extremely complex molecular behaviour and express trophoblastic, ectodermal, endodermal and mesodermal cells, specific regulators. There are embryonic pluripotent like stem cells, which are distinct from both embryonic and induced pluripotent stemcells have the propensity to be reprogrammed into a primitive fully functional pluripotent stem cell.

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Conflict of Interest : None

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Original Article

Effects of Pranayama on Short Term Memory (Visual & Verbal)

Gaurav Srivastava[1], Richa[2], Mythali Bhaskaran[3]

Abstract

Aim and Objective : Our aim is to evaluate changes in short term memory (verbal and visual) after a practice of Pranayama only, for duration of 40 days in two sessions a day of 20 minutes each. Also to see if there is a change, is it verbal or visual memory which shows a significant improvement.

Materials and Method : This study was conducted in the Physiology Department Yoga Center on 17 volunteer subjects (age 18 years to 20 years). Pranayama training was given to them for one week and were asked to practice the same in two sessions, one at 6 am in the morning and the second at 4 pm in the evening everyday under observation, for 40 days. During the course these individuals were subjected to various memory assessment before and after Pranayama training.

Observations : The results showed Benton Visual Retention Test which evaluate the short term visual memory has shown a highly significant improvement in the scores after the Pranayama session.

Results : Our results shows that there is a definite improvement in short term memory mainly in visual memory though there was not any changes in their auditory memory.

Conclusion : Pranayama is recommended for all the medical students during their study period to improve their performance.

Key words : Blender Gestolt Test, Benten Visual Retention Test, Reys Complex Figure Test, Paragraph Repetition Test, Paired Associate Learning.

Yoga is well known for its contribution towards maintenance of normal health since the Vedic period. The term 'Yoga' is derived from Sanskrit word 'Yug' which literally means a union of body and mind . Yoga includes Asanas, Pranayamas, Mudras and Nandanusadhana. Prayanam is practice in sitting position and is very complex act. In this practitioner inhales and exhales air slowly, deeply and completely and also stop breathing intermittently every minutes.

When we breadth in, O_2 in extracted from air and is transferred to blood from alveoli of lungs. In blood O_2 combines with Hemoglobin and is transported to various organs and get released their according to the need of cells in organ . Brain requires more Oxygen than any other organ and any reason for lack of Oxygen result in loss of mental balance, concentration and control over emotions.

Yoga is one of the mean by which memory can be enhanced. As observed by Yogacharya Vishwa. V Yoga Vidyapeeth Nasik[1] that Omkar Chanting produce vibration in the spinal cord that increase memory and concentration. Murphy and Punovan[2] have received that behavioural effects, cognitive ability, concentration, attention and memory shown to improve with Meditation and Yoga practice.

Shirly Telles[4] demonstrate that people between age of 18 to 45 years have shown improved reversal ability, eye hand co-ordination and accuracy on one month Yoga practice. Naveen[5] proved in 108 children aged between 10 to 17 years have improved verbal and spatial memory on Yogic practice. These studies have proved that short term memory has improved on Yoga practice even for a short period.

Editor's Comment :

- It is for education of Society so as to use Deep Breathing Exercise for better Mental & Physical Health.
- Many psychological test has been done elaborate the result.
- Visual memory & verbal both increases by Deep Breathing Exercise.
- Do follow the advice for better development of whole self.

Material and Method

This study was conducted in the Yoga Center of our Medical College Physiology Department. This project was approved by the Institutional Ethics Committee.

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A code was provided to the subjects to keep their identity closed. Their achievement scores were not disclosed to anywhere. Result of our scores where used only for this research. This study was conducted on 17 young healthy MBBS students of either gender having good general physical condition with age group of 18 to 20 years with average Body Mass Index with their written consent.

Student with the history of Hypertension, Smoking, Alcohol intake, Chronic lung and Cardiovascular disease or any one a Sports person or practicing Yoga we are not included in the study.

Students were given at the 1 week of project the Pranayama training. They were asked to practice the same in two session one at 6:00 AM morning and second at 4:00 PM in the evening everyday under observation for next 40 days for 20 minutes session each. They were subjected to memory assessment before and after Pranayam training. The memory test for verbal and visual memory used before and after Pranayam training course were Blender Gestolt Test, Benton Visual Retention Test, Rey Osterrieth Complex Figure, Paragraph Repetitions and Paired Associated Learning. The data was analysed by T-test using statistical software package.

Observations

Table 1 shows that after 40 days of Pranayama training the out come of the score in Bendergestolt Test is not statistically significant (p=0.21) though there have been an increase in the scores from 6.12±1.21 to 6.76±1.43.

Table 2 shows comparing the scores of the pre with the post test it is seen that the difference is highly significant in Benton Visual retention test (p = 0.001).

From Table 3 in REYS TEST it is observed that after pranayama the number in “above average” category has increased from 4-12 ie, there is a significant change in post test performance when compared to the pre-test.

The Table 4 has shown that after 40 days of Pranayama training there is no significant change in scores in the Recall Immediate Test (p = 0.78) which is a test to evaluate verbal memory.

While comparing the scores in the paired associate learning it is found that though there is no statistical significance (p=0.12) there is a marked difference in the values between the pre and post scores (Table 5).

Table 1 — *Comparison of Pre & Post Test score in Bendergestolt Test*

N=17	Mean	STD Deviation	Paired t-test
Pre-Test	6.12	1.21	t = 1.33
Post Test	6.76	1.43	P = 0.20 Not Significant

Table 2 — *Comparison of Pre & Post Test score in Benton Visual Retention Test*

N=17	Mean	STD Deviation	Paired t-test
Pre-Test	6.06	1.43	t = 5.49
Post Test	8.41	0.87	P = 0.001 Highly Significant

Discussion

The short term memory both visual and verbal was evaluated in 17 young health volunteers undergoing MBBS course in Stanley Medical College of age 17-21 years after a practice in Pranayama (both nostrils open) for 6 weeks.

On analysis of our results it was observed that in:

Bender Gestalt Test, a test to evaluate spatial or visual memory though the scores between the pre and post test values were not significant there has been an increase in the score values.

In Benton Visual Retention test which again evaluate the short term visual memory has shown a highly significant improvement in the scores after the Pranayama session.

The third test performed to evaluate the spatial memory is the Reys Osterieth Complex Figure Test. The judgement is done as belonging to and below average, average and average depending on the

Table 3 — *Comparison of Pre & Post Test score in Reys Test*

Reys	Below Average	Average	Above Average
Pre-Test	13	0	4
Post Test	0	5	12

Table 4 — *Comparison of Pre & Post Test score in Recall Immediate Test*

N=17	Mean	STD Deviation	Paired t-test
Pre-Test	26.18	4.76	t = 0.29
Post Test	25.65	5.04	P = 0.78 Not Significant

Table 5 — *Comparison of Pre & Post Test score in Paired Associate Learning*

N=17	Mean	STD Deviation	Paired t-test
Pre-Test	11.88	3.39	t = 1.45
Post Test	13.14	1.36	P = 0.17 Not Significant

performance. The more number of students fell into the above average performers after the Pranayama session [From 3(pre) to 12(post)].

In the above three test the visual spatial and constructional abilities are all considered together as the candidate draws designs immediately from memory and these are related to the right hemisphere. It has been shown that subjects concentrating on 2 attributes of a visual stimulus show activation of the right angular cortex. Therefore the right hemisphere is superior to the left. In discriminating the spatial patterns milner hemisphere specialization[7] and hemisphere function in sorbon[8].

Naveen, *et al*[5] in their study on memory with Pranayama have also documented in improvement in spatial memory. Manjunath NK and Shirly Telles[4] of Swami Vivekananda Yoga Research Foundation in their study on spatial memory after Yogasana (90 minutes per day) with Pranayama and Meditation (60 minutes per day for 10 days along with listening to meaningful stories and devotional sessions found an improvement compared with the controls who did not undergo such sessions. Our test results with verbal memory either Recall Immediate Test or the paired associate learning did not show a change which was statistically insignificant.

The study mentioned earlier have also reported not a significant change in the verbal memory.

Nagrathna, *et al*[5] in their study have worked as a larger group (108) of subjects belonging to 11-16 years best have found an improvement unusual and not in verbal memory. Our results therefore resemble those of the above studies.

Medical students from the first to the final year of their study through their study internship are exposed to extreme large load of study material and the effort given by them is almost 12 hours per day the students have a high anxiety state due to lack of sleep and inability to match the demand and effort. They have little time for extra-curricular activities and their learning includes observational skills (in the form of signs presented by patient) though psychomotor and analytical skills are also very important.

Pranayama is a simple technique which can be practiced for a short duration and no special infrastructure facilities are necessary for the practice. Improving the visual memory with such sessions a medical student can better his / her observational skills during their study period.

Any form of Yoga whether the Asanas, Pranayama, or Meditation are already known to reduce the level of anxiety.

A medical student should be recommended to practice Pranayama every day to improve his/her performance and allay his/her anxiety during his/her study period.

Conclusion

Short term memory (visual and verbal) were evaluated on 17 young healthy MBBS students of age between 17-21 years after 6 weeks of pranayama practice.

Our results shows that there is a definite improvement in short term memory though there was not any changes in their auditory memory.

Pranayama is recommended for all the medical students during their study period to improve their performance. An evaluation of the performance in the clinical subject after Pranayama needs to be carried out to confirm our statement.

Ethical Clearance : This study was approved by Institutional Ethics Committee.

Source of Support : Nil.

Conflict of Interest : None.

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Original Article

MRI in Assessing the Most Common Cause of Shoulder Joint Pain

Rakshitha C[1], Harshith C S[1], Vishwapremraj D R[2]

Abstract

Background : Shoulder pain and reduced function are common complaints in an old patient and in a young patient following trauma in an Outpatient Department (OPD). The symptoms are often related to the unique anatomic relationships present around the shoulder joint. Impingement of the rotator cuff and adjacent bursa between the humeral head and the coracoacromial arch are among the most common causes of shoulder pain. MRI is an ideal imaging modality for pathologies of the shoulder joint.

Key words : Shoulder Joint Pain, Role of MRI ,Rotator Cuff Injuries.

Shoulder pain and functional limitations are common complaints, especially among older adults and young patients following trauma, often due to the complex anatomical relationships around the glenohumeral joints. Pathologies such as rotator cuff impingement between the humeral head and coracoacromial arch are key contributors to these symptoms. Magnetic Resonance Imaging (MRI) stands out as the ideal modality for evaluating soft tissue injuries of the shoulder, surpassing other imaging techniques in accuracy and detail. This study aims to assess the role of MRI in diagnosing causes of shoulder pain and to identify the most frequently affected anatomical structures in patients presenting with shoulder complaints (Figs 1-9).

Aims and Objectives

To evaluate the role of MRI in imaging soft tissue injuries of shoulder joint.

To ascertain the most common cause of pain in shoulder joint.

Materials and Methods

MRI images depicting soft tissue pathologies of shoulder joint stored in MEDSYNAPSE database in Department of Radiodiagnosis, SIMS&RC, Bangalore were retrospectively reviewed with retrieval of data.

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Editor's Comment :

- MRI is a highly effective tool for detecting soft tissue pathologies in the shoulder, making it the preferred choice for clinicians.
- Supraspinatus tendon injuries are the most prevalent cause of shoulder pain, with isolated and combined tendon pathologies commonly observed.
- Labral injuries and biceps tendinopathy are also frequently noted, especially following trauma, while deltoid involvement is rare.

Results

A total of 65 cases with shoulder pain were evaluated retrospectively from the MEDSYNAPSE data base in the Department of Radio-diagnosis at SIMS&RC, Bangalore.

Majority of the cases showed the most commonly involved structure in case of shoulder pain was supraspinatus tendon. Isolated cases of supraspinatus tendon pathologies were also a common finding. Few of the cases showed pathology in the supraspinatus, infraspinatus tendon and subscapularis following trauma. The involvement of all the rotator cuff muscles and the biceps tendon was noted in a case of severe trauma. Biceps tendinopathy was a common non-specific finding in majority of the cases. Labral injuries

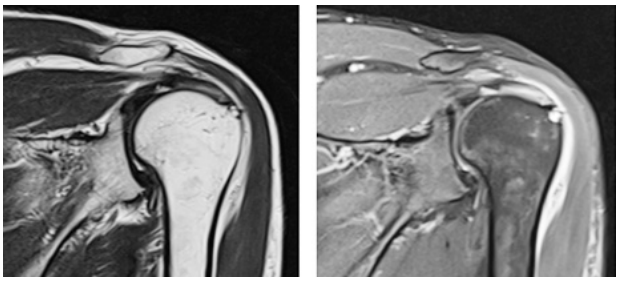

Fig 1 — Coronal T2WI (a) and coronal PDFS (b) showing partial thickness articular surface tear of supraspinatus tendon.

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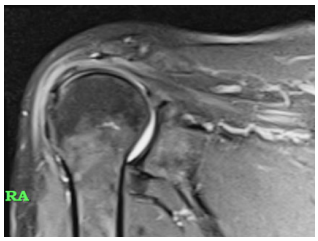


Fig 2 — Coronal PDFS image showing a rim rent tear at the site of insertion of supraspinatus tendon.

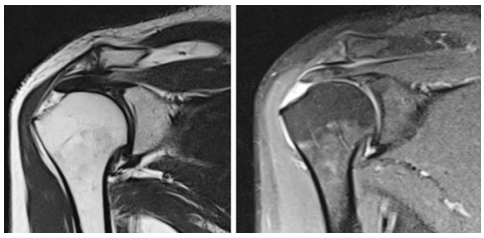


Fig 3 — Coronal T2WI (a) and coronal PDFS (b) showing complete tear of supraspinatus tendon with retraction of fibers and fluid collection along the insertion site.

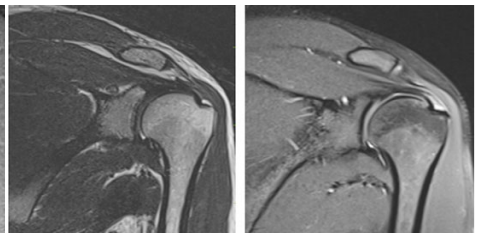


Fig 4 — Coronal T2WI (a) and coronal PDFS (b) showing foot print tear of supraspinatus tendon at the insertion site.

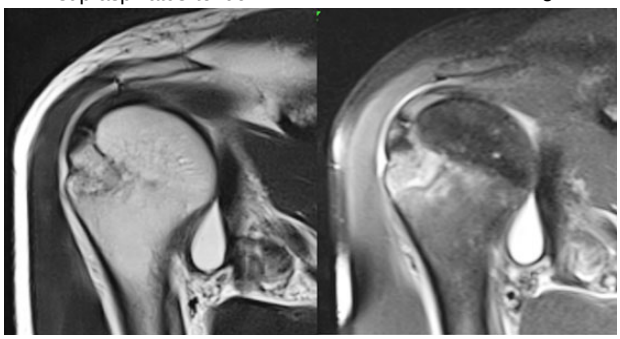


Fig 5 — Coronal T2WI (a) and coronal PDFS (b) showing full thickness tear of the supraspinatus tendon extending from the articular surface to the bursal surface with mild retraction of the tendon and presence of fluid in between the tear. Presence of fluid in the inferior axillary pouch is also noted with mild joint effusion.

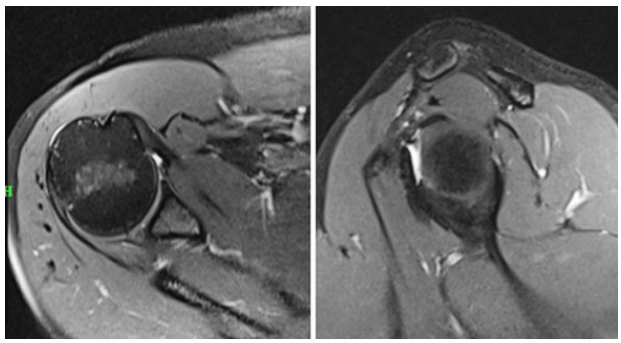
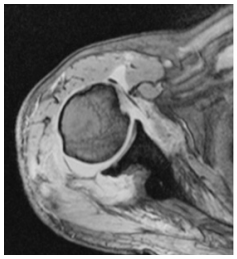


Fig 6 — Case 6: Axial PDFS (a) and sagittal PDFS (b) showing type II SLAP tears.



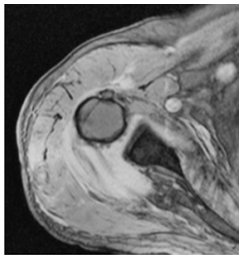
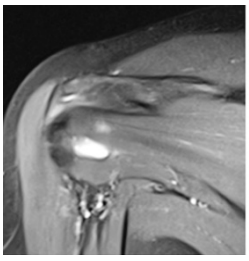


Fig 7 — Axial PDFS (a): biceps tendon is not seen in the proximal aspect of bicipital groove. Axial PDFS (b): further down section images show mildly oedematous biceps tendon with wavy pattern.



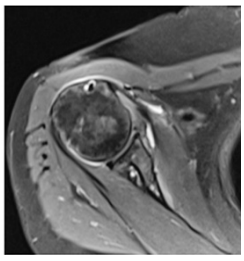


Fig 8 — Coronal PDFS (a) and axial PDFS (b) images showing hyperintense signal along the insertion site of infraspinatus muscle.

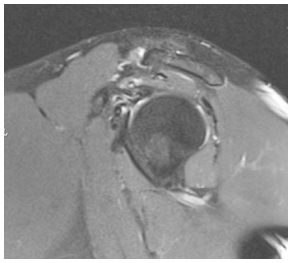


Fig 9 — Sagittal PDFS image (arrow) showing type III acromion impinging on supraspinatus

were a common finding after a traumatic event. Deltoid muscle was rarely involved in any pathology. The involvement of infraspinatus, subscapularis, teres minor, labrum and deltoid were never seen without the involvement of supraspinatus pathology.

Discussion

Pain and reduced mobility of the shoulder is one of the most common complaints following trauma or in old age. These symptoms are often related to the unique anatomical relationships present around the glenohumeral joint.

Anatomical variations in the shape of the acromion, degenerative changes of the rotator cuff tendons with or without calcifying deposits, repetitive mild trauma or severe trauma, chronic overuse due to occupation or sports activities are among the most common causes resulting in pathology of the rotator cuff muscles by increasing the friction against the acromion or the coracoacromial arch resulting impingement of the rotator cuff and adjacent humeral head and coracoacromial arch resulting in pain around the shoulder joint[1].

The rotator cuff muscles are the most commonly involved anatomical structure which are responsible for causing shoulder pain. Ultrasound (USG) and Magnetic Resonance Imaging (MRI) can be used for evaluating the cause of shoulder pain. Shoulder ultrasound has a reasonable amount of accuracy in detecting pathologies of the rotator cuff structure

however the learning curve is relatively longer and the findings are usually subjective hence, MRI is preferred over USG and is considered as the investigation of choice in assessing soft tissue pathologies around the shoulder joint[2]. Shoulder arthrography is considered as the gold standard for assessing the shoulder joint however being an invasive procedure is not done on a regular basis unless and until absolutely required.

Rotator cuff is composed of tendons of the subscapularis, supraspinatus, infraspinatus and teres minor, all of which have a common insertion in the head of the humerus. The main function of rotator cuff is to provide stability to the shoulder joint. Rotator cuff injuries are most commonly encountered pathologies around the shoulder joint.

The various types of acromion are Type I (flat), Type II (curved), Type III (hooked) and Type IV (convex). Type III and IV cause impingement over the rotator cuff structure resulting in pain. Subacromial Impingement Syndrome is a painful compression of the supraspinatus tendon, subacromial-subdeltoid bursa and long head of biceps tendon between the humeral head and anterior portion of the acromion during abduction and forward elevation of the internally rotated arm resulting in pain. There are 3 stages of impingement, Stage I where there is edema and hemorrhage, Stage II in which there is fibrosis and thickening of the tendons and stage III in which there is progressive impairment of function due to degeneration and rupture of tendon.

Other causes of shoulder pain include narrowed subacromial space, os acromiale which occurs due to non-fusion of the ossification centres of the acromion, supraspinatus hypertrophy due to sports activities and acromio-clavicular joint osteoarthritis.

Rotator cuff tears are the most commonly encountered pathologies around the shoulder joint which can occur either due to trauma which is most common in young age or due to degenerative changes resulting in subacromial impingement which is common in old age.

Types of Rotator Cuff Tears are[3] :

(i) Partial thickness tears: include articular surface tears, bursal surface tears and inter-substance tears

(ii) Full thickness tears: include incomplete full thickness tears, complete full thickness tears, complete full thickness tears with retraction, complete full thickness tears with retraction and muscle atrophy. Muscle atrophy is classified as mild, moderate or severe based on the tangent sign.

The tears are best visualised on coronal proton density and T2 weighted imaging sequences.

Tendinosis also known as tendinitis or tendinopathy is the second most common cause of shoulder pain which occur due to degeneration of the of the tendons which appear as thickening of the tendon with myxoid changes and edema which is better visualized on proton density sequences.

Rotator cuff arthropathies are a pattern of joint degeneration which occur due to loss of stabilizing function of the rotator cuff tendons. The imaging findings include reduction of acro-humeral distance, acetabularization of coraco-acromial arch, narrowing of glenohumeral; joint and humeral head necrosis with collapse of humeral head[4].

The most commonly affected structure in decreasing order are supraspinatus, biceps, infraspinatus, subscapularis, teres minor.

Superior labral anterior posterior injuries are usually associated with injuries to the rotator cuff structure and rarely occur in isolation.

Conclusion

The study reinforces the value of MRI in the evaluation of shoulder pain, providing detailed insights into soft tissue injuries that often escape detection by other imaging modalities. Supraspinatus tendon is most commonly implicated, with rotator cuff and labral injuries frequently seen after trauma or in degenerative conditions. These findings highlight the importance of early and accurate MRI-based diagnosis to guide management and improve patient outcomes in shoulder pathology.

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Original Article

Monocyte to HDL Ratio (MHR) as an Early Predictor of Diabetic Retinopathy in Diabetes Mellitus

Pankaj Kumar Jain[1], Rajesh Yadav[2], Datar Singh[3], Sachin Kumar[3]

Abstract

Aims and Objective : To study Monocyte to HDL ratio (MHR) as an early predictor of Diabetic retinopathy in patients of Diabetes Mellitus.

Methodology : A total of 105 Diabetes Mellitus patients, 50 of whom had Diabetic retinopathy and 55 without diabetic retinopathy and 50 healthy controls were included in this cross-sectional study. Monocyte to HDL ratio was calculated by blood sampling after Fundus examination on all subjects.

Result : Monocyte to HDL ratio was higher in Diabetes Mellitus patients with Diabetic retinopathy compared to both the control group and without Diabetic retinopathy (p=0.00025). There was a significant positive correlation between Monocyte to HDL ratio and Diabetic retinopathy (r=0.26, p=0.001).

Conclusion : This study showed that patients with Diabetes Mellitus may be more likely to develop Diabetic retinopathy when they have high Monocyte to HDL ratio values. Based on this result Clinicians can also use Monocyte to HDL ratio as a new laboratory marker to predict Diabetic retinopathy at early stage.

Key words : Diabetes Mellitus, Diabetic Retinopathy, Monocyte to High Density Lipoprotein Ratio.

Diabetic Retinopathy (DR) constitutes a significant portion of visual impairments. It develops due to the destruction of capillaries, venules and arterioles in the retina caused by hyper-glycemia or insulin deficiency[1]. The prevalence of retinopathy is 35%[2]. The pathogenesis of Diabetic retinopathy is complex, with inflammation playing a crucial role in its development and progression, alongside factors such as hyper-glycemia and hypertension[3-6].

Diabetic retinopathy is one of the most significant diabetic microvascular complications and a leading cause of irreversible blindness among the working-age population Worldwide[7]. Various inflammatory cytokines and chemokines, such as ICAM-1, IL-1β, IL-6, IL-8, TNF-α, and MCP-1, have been found to be elevated in the serum, vitreous, and aqueous humour of diabetic patients with Diabetic retinopathy[8].

Monocytes releases proinflammatory cytokines at sites of inflammation, thereby influencing the severity of inflammation. This makes them an important inflammatory biomarker[9]. Additionally, plasma High-density Lipoprotein (HDL) cholesterol inversely correlates with DR risk[10,11] and has antioxidant properties that protect endothelial functions[12,13].

Editor's Comment :

- MHR serves as a simple and reliable indicator of systemic inflammation and is significantly associated with the presence and progression of Diabetic retinopathy.
- It may be utilized as an early predictor for Diabetic retinopathy in diabetic patients at resource limited settings.

The monocyte count to HDL ratio (MHR) can reflect the inflammatory status and is related to the development of diseases associated with chronic inflammation. MHR has been linked with the occurrence and prognosis of cardiovascular diseases, diabetic nephropathy and diabetic peripheral neuropathy[14-17]. In this context, the present study aims to investigate the associations between MHR and the prevalence of Diabetic retinopathy in adults with Diabetes Mellitus.

Materials and Methods

Study Population :

This cross-sectional study was conducted between 23/12/2023 to 23/06/24. A total of 105 patients, 50 of whom had Diabetic retinopathy, were included in the study. The control group consisted of 50 healthy individuals who are matched in terms of age and gender.

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Participants who accepted to participate in the study were questioned in terms of age, gender, drug history, personal history like smoking, alcohol, past and family history.

Old ischemic disease, Old cerebrovascular accident, Haematological disease, Malignant disease and Autoimmune disease were excluded from the study.

Clinical Examination and Biochemical Analysis :

The diagnosis of DM was made according to the American Diabetes Association guidelines[18]. After fundoscopic examination was applied to all participants, the diagnosis of retinopathy was made. DR was diagnosed if any characteristic lesions existed as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). Peripheral venous blood samples were taken on OPD basis or within 24 hours of admission. Complete Blood Count including Monocyte count will be measured by an automated haematology analyser (Sysmex XS-800i, Japan) and manually corrected by pathologist to overcome by any technical error.

Routine biochemical test- Liver Function Test, Renal Function Test and Lipid Profile was performed by automated biochemistry analyser (Erba Mannheim EM-200 or Erba Mannheim XL-640).

Neutrophil/Lymphocyte Ratio (NLR), Monocyte/ Lymphocyte Ratio (MLR), Platelet/Lymphocyte Ratio (PLR) and MHR were calculated and recorded for each participant.

Statistical Analysis :

In all statistical analyses, SPSS 26.0 Statistical Package Program for Windows (SPSS Inc, Chicago, IL, USA) was used. The Kruskal-Wallis test, one-way ANOVA, and Fisher's exact test were used to compare the groups. The numeric variables as mean± SD and median (minimum-maximum) and the categorical variables as number and percent were expressed. Point biserial was applied to evaluate the correlation between the presence of DR and other parameters. Logistic regression analysis was used to calculate predictors of DR. MHR cut of value was calculated by Receiver Operating Characteristic (ROC) curve analysis to predict DR. A p-value of <0.05 was accepted as statistically significant.

Results

The study included 155 subjects, comprising 88 males (56.77%) and 67 females (43.22%). A statistical difference was observed among the three groups concerning gender, Total Leukocyte Count, Neutrophil Count, Platelet Count and HDL levels. Additionally, a statistical difference between groups 2 and 3 was noted in terms of insulin and statin use.

Statistically significance was found among all three groups for Haemoglobin, Lymphocyte count, Monocyte Count, HbA1C, Creatinine, Total Cholesterol, Triglyceride, NLR, MLR, PLR, and MHR (Table 1).

Positive correlations were identified between DR and HbA1C (r=0.49, p=0.001), monocyte count (r=0.2, p=0.014), Total Cholesterol (r=0.23, p=0.004) and MHR (r=0.26, p=0.001) (Table 2).

Regression analysis indicated that MHR is an

Table 1 — *Baseline characteristics and laboratory parameters of groups*

Parameter	Control (Group 1)	Without Dr (Group 2)	T2DM with Dr (Group 3)	P-Value
Age (Years)	49.7±19.29	53.76±14.82	56.64±12.5	0.09
Male n (%)	30 (60%)	28 (50.9%)	30 (60%)	0.55
Insulin n (%)	-	5 (9%)	6 (12%)	0.753
Statin n (%)	-	6 (10.90%)	9 (18%)	0.40
Hemoglobin (g/dl)	11.85 (5-16.2)	12.1 (6.6-17.6)	10.95 (6.3-16.1)	0.016
Tlc (10^3 µl)	9.07 (17-21)	8.1 (3.7-20.4)	7.5 (2.2-27)	0.804
Neutrophil (10^3 µl)	7 (0.8-20.530)	4.9 (1.8-20)	5.3 (1.1-24.12)	0.143
Lymphocyte (10^3 µl)	2.83 (0.63-8)	2.04 (0.27-4.6)	1.7 (0.30-3.93)	0.001
Monocyte (10^3 µl)	0.30 (0.09-0.73)	0.33 (0.09-1.37)	377.5 (0.08-1.6)	0.0016
Platelet (10^3 µl)	263 (23-625)	497 (390-536)	272 (180-587)	0.94
HbA1c (%)	5.7 (5-6.2)	8.2 (5.1-18.5)	10 (6-16.8)	0.00001
Creatinine (mg/dl)	1 (0.4-1.5)	0.9 (0.6-2.4)	1.1 (0.5-2.3)	0.00818
Cholesterol (mg/dl)	120.5 (61-240)	160 (65-292)	159.5 (59-371)	0.00004
Triglyceride (mg/dl)	95 (40-291)	142 (38-716)	148 (58-856)	0.00001
HDL (mg/dl)	46.5 (20-73)	40 (13-99)	40 (16-92)	0.1779
NLR	2.30 (0.5-3.44)	2.36 (0.54-74.07)	3.22 (1.09-22.33)	0.00023
MLR	0.12 (0.02-6.42)	0.14 (0.02-0.78)	0.21 (0.02-1.57)	0.0001
PLR	89.76 (18.37-586.25)	126.73 (10.42-518.75)	154.16 (0.11-660)	0.00015
MHR	6.18 (2.85-33)	8.46 (2.74-41.5)	11.01 (2.3-72.72)	0.00025

independent predictor of Diabetic retinopathy (Table 3).

ROC curve analysis for MHR showed that area under curve was 0.671 and p=0.004 Significance value (Fig 1).

Discussion

In the present study, differences in MHR were observed across all three groups. MHR was higher in patients with Diabetes Mellitus with DR compared to those without retinopathy and healthy controls. Additionally, MHR was found to be an independent predictor of DR.

Inflammation markers and monocytes play a crucial role in the development of diabetic complications[16]. Chronic retinal inflammation significantly contributes to the development of DR[7]. Monocyte levels increase in the retinal vessels, where they differentiate into macrophages that secrete inflammatory cytokines and growth factors, adhering to the outer surface of retinal capillaries. This leads to the breakdown of the blood-retinal barrier, increased retinal vascular permeability, and capillary non-perfusion, which are characteristic pathological features of early DR. Despite the known role of monocytes in DR development, studies have shown no direct relationship between blood monocyte count and DR[19]. Our study supports this evidence, finding that monocyte counts were significantly increased in patients with DR compared to healthy controls and patients without DR, aligning with previous findings. Hyper-glycemia enhances the inflammatory status, leading to the release of more neutrophils and monocytes from the bone marrow, which are then recruited into the retinal vessels, causing damage[20].

Table 2 — *Correlation of presence of diabetic retinopathy with other parameters*

Parameter	r	P
Age	0.14	0.079
Hemoglobin	-0.16	0.044
TLC	0.1	0.238
HbA1c	0.49	0.001
Neutrophil	0.06	0.472
Lymphocyte	-0.05	0.556
Monocyte	0.2	0.014
Platelet	0.01	0.928
Cholesterol	0.23	0.004
Triglyceride	0.1	0.199
HDL	-0.13	0.094
NLR	-0.07	0.41
MLR	-0.05	0.563
PLR	-0.03	0.722
MHR	0.26	0.001

Table 3 — *Univariate regression analyses to identify predictors of Diabetic retinopathy*

Parameter	Odd Ratio	95% C I	P
HbA1c	0.67	0.58-0.78	0.001
Monocyte	1	1-1	0.021
Cholesterol	0.99	0.98-1	0.006
MHR	1.07	1.02-1.12	0.004

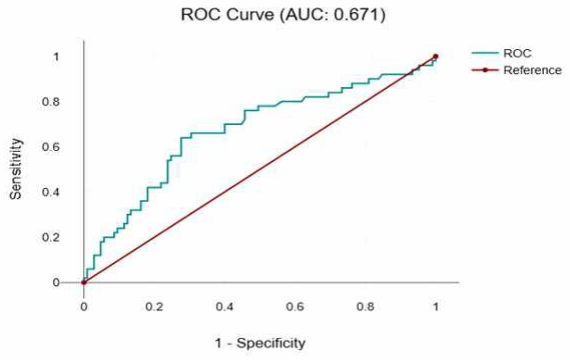

Fig 1 — *Receiver Operating Curve (ROC) analysis for MHR as a predictor of DR*

HDL transports cholesterol from peripheral tissues to the liver, prevents the harmful effects of LDL and reduces LDL oxidation. Furthermore, HDL inhibits monocyte activity, prevents monocytes from differentiating into macrophages, and limits the inflammatory response. It prevents endothelial dysfunction by removing cholesterol from lipid-loaded macrophages in atherosclerotic lesions. Lyons, *et al* study with 988 people showed that low HDL levels are a risk factor for DR[21]. Evidence indicates that poor control of triglycerides and LDL is associated with the incidence and progression of DR, while higher HDL levels and the use of lipid-lowering medication significantly reduce DR risk[22]. In our study, triglyceride levels were higher in the DR group compared to the other two groups, and HDL levels were higher in the control group compared to the other two groups. There was no difference in HDL levels between the T2DM with DR and without DR groups.

Considering the pro-inflammatory effects of the monocyte-macrophage system and the anti-inflammatory effects of HDL, combining these two parameters into a single inflammatory marker (MHR) is logical. Previous studies have shown that MHR is associated with many inflammatory diseases, particularly cardiovascular diseases. MHR has also been studied in DM and its complications, with high MHR linked to peripheral neuropathy, a common complication[14-17]. In our study, high MHR rates were observed in T2DM patients with DR, but not in those

without, suggesting that MHR can be used as a marker of inflammation and endothelial dysfunction for the development of DR. Recently, the ratios of these parameters (NLR, MLR, PLR, etc) have been defined as new inflammatory markers and are frequently studied in inflammation-related diseases[23]. Our study has shown that NLR, MLR, and PLR values are high in DR.

Moreover, compared to other expensive inflammatory markers, such as interleukin factors IL-1, IL-6, tumour necrosis factor-α, and monocyte chemo-attractant protein-1, the MHR can be easily calculated from a simple blood analysis, making this index more practical, cost-effective, and useful for predicting DR[8].

Conclusions

MHR was higher in patients with T2DM with DR compared to without retinopathy and healthy controls as well as there was positive correlation of MHR with DR. Also, MHR was determined to be an independent predictor of DR.

Based on these results, MHR could be an early predictor biomarker for DR.

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Review Article

Changing Scope of Medical Writing in the Era of Artificial Intelligence — A Fresh Perspective

Subhrojyoti Bhowmick[1], Mahasweta Gangopadhyay[2], Arpan Ganguly[3], Ankita Roy[4], Anirban Dalui[5]

Abstract

Background : Artificial Intelligence (AI) is considered useful for improving various functions in healthcare delivery and clinical decision-making, including its use as prognostic and a diagnostic aid, which ultimately decrease the healthcare delivery time.

Material and Methods : The effects of the recent disruption caused by Large Language Models (LLMs) and AI chatbots such as ChatGPT on the functions and roles in the pharma industry have received limited attention, despite the chatter regarding its safety. Multiple facets of medical AI include data analysis, using machine learning, deep learning, natural language processing, LLM training, chatbots, domain-specific LLM creation and Bidirectional Encoder Representations from Transformers (BERT) software development. These AI products aim to reduce productivity timelines and increase the utilities of large clinical datasets, especially in regulatory and clinical documentation support. The extent of assistance provided by AI-based literature survey tools and LLM based medical writing require discussion and vigilance. AI has disrupted research functions and boosted pharmaceutical product development timelines by a potential decrement of timeline costs, the utilization of AI is being probed in drug discovery, development, and regulatory submissions. Considering this disrupted scenario, this review throws light upon the advent of AI and the responses from regulators, publishers, and the EQUATOR NETWORK.

Discussion : The authors intend to inform the medical writing fraternity regarding the areas of risks and benefits of using AI tools in medicine.

Conclusions : The pharma industry grapples with a routine dependence on AI, a surge in the vigilance, ethical considerations and robust governance has been observed.

Key words : Artificial Intelligence, Language Learning Model, Machine Learning, Medical Writing.

Artificial Intelligence (AI) involves all processes using computers, data storage, and data processing devices that produce robust computer-generated outputs from analysing large volumes of data generally similar to the analytical tasks performed by humans. AI involves storage, processing, analysis, and critical scrutinizing of data and creating an AI system that begins with feeding existing data into the computer system and allowing it to “learn”.

Editor's Comment :

- It is mandatory to uphold the principles of transparency, inclusion, accountability, trust, and patient safety in all processes of the drug and medical device development lifecycle, as per the EMA and FDA directives.
- The EQUATOR NETWORK guidelines adequately assess AI in medicinal evaluation and reporting.

Material and Methods

For the literature review, open access articles were sourced from indexed databases like PubMed Central, EMBASE, JSTOR, Directory of Open Access Journals (DOAJ) and studied extensively.

From the initial 100 articles screened, a total of 50 were shortlisted for drawing insights on the practical use of AI in medical research and writing in the pharmaceutical industry.

In preclinical research, AI and Machine Learning (ML) systems are commonly used for data models that can replace, reduce, and/or refine the processes of testing, identification, re-evaluation, and other procedures. Across numerous medical specialties, AI aids in medical decision-making through expediting steps involved in molecular testing and reducing the

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costs of drug discovery[1].

ChatGPT enables the retrieval of preliminary molecular data/information regarding pertinent drug targets, setting off the discovery pathway for specific diseases that require further studies to be validated. A plug-in present in ChatGPT-4 is noted to be potentially helpful for these niche purposes[2]. Moreover, such AI platforms may help comprehend drug target proteins, molecular binding dynamics, antigen activity, three-dimensional and two-dimensional structural domains of proteins, and extract information of active sites of drug targets. In addition, ChatGPT is expected to assist in understanding the ADMET properties (absorption, distribution, metabolism, excretion, and toxicity) of investigational new drugs and be useful for toxicity assessments[2].

LLMs are large datasets of information stored in computers in conversational English language, which is different from machine language or programming languages. The development of LLMs has given rise to a new domain in information analytics known as Natural Language Processing (NLP), which involves algorithmic programming of the LLMs. These developments have been significant for the early-stage drug discovery researchers who may want to use LLMs like ChatGPT in retrieving information from large web databases using specific prompts. However, these approaches need testing and validation. A domain-specific LLM named "DrugChat" has been developed for the pharma and life sciences industry, which has an interface and user-friendliness as that of ChatGPT that can extract information on drug molecules.

Since there is currently minimal supervision of the application of rapidly developed AI tools in medicine it may affect the quality of medical documents. This in turn highlights the potential limitations of AI in medicine, including challenges spanning ethical, legal, regulatory, methodological, and technical domains. Hence, a powerful governance model has been proposed by the European Medicines Agency (EMA), under the European Commission.[3] These efforts of the EMA to control the use of AI are considered a small step as part of the BIG DATA Workplan 2022-2025, under development by the Big Data Steering Group, a functional collaborative under the EMA[4].

Application of AI Tools in Clinical Research :

Perspectives from the insiders of the pharmaceutical industry have highlighted pitfalls such as implicit bias, reproducibility, and clinical validity, which need to be addressed. Stricter methods for the validation and evaluation of AI development tools are necessary. Specific guidelines were thus developed to address all concerns raised by regulators and vigilantes using relevant research literature of biostatistics and data sciences. These were published alongside the guidance document published by the United States Food and Drug Administration (USFDA)[4] and the reflection paper given by the EMA[5,6]. Fourteen documents (Table 1)[7-20] are available : the Guidelines for Developing and Reporting framework[7], AI in Health Care[8], CONSORT-AI[9], SPIRIT-AI[10], DECIDE-AI[11] (Table 1). Among these frameworks, the Guidelines for Developing and Reporting framework by Luo W, *et al*[7] and AI in Health Care[8] publication elucidate the general guidance on the use of AI in medicine.

TRIPOD-AI and PROBAST-AI Statement :

In 2015, the "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement" was published[14]. While most items in the TRIPOD Statement are relevant to ML based prediction model studies and as most ML methods originate from statistical methods, two overlapping prediction modelling scenarios have emerged in the statistical and epidemiological domains. The relative novelty of applying ML methods to clinical prediction modelling had conferred some uncertainty regarding the credibility of these recent studies. Therefore, the TRIPOD group initiated the development of a consensus-based extension of the TRIPOD statement specifically focused on reporting of studies that undertake the development, validation or updating of a diagnostic or prognostic prediction model using ML techniques known as TRIPOD-AI[12].

The TRIPOD-AI extension comprises a checklist and an accompanying elaboration and explanation document, which informs regarding the minimal set of items to report with detailed examples of good reporting for each item.

In addition, the Prediction Risk of Bias Assessment Tool (PROBAST) was published in 2019 to critically appraise the study design, conduct and analysis of prediction modelling studies. PROBAST comprises four domains (participants, predictors, outcome and analysis) and contains 20 signalling questions to assess the risk of bias[15]. Clearly, the processes of "risk of bias" and reporting are intrinsically linked, as this is a predication made on primary data.

Table 1 — *All available audit frameworks established to control the usage of AI tools in clinical medicine, medical publishing, data analysis, and scientific reporting*[1]

Guideline/Framework	Summary	Intended user entities
Guidelines for Developing and Reporting	12-item guidance list for applying and reporting the medical AI Amodel specifications and results in biomedical research.	AI developers, investigators
AI in Healthcare	A general paper describing the challenges and opportunities for medical machine learning (MML) and AI.	AI developers, clinicians, patients, policymakers
CONSORT-AI	A structured reporting framework for specific clinical trials that evaluate medical treatments having an AI component (25 core and 15 AI-specific reporting items)	AI modelling software developers, investigators
Standard Protocol Items: Recommendations for Interventional Trials-AI Extension (SPIRIT-AI)	Guidance framework for writing clinical trial protocols for studies that evaluate medical AI interventions (25 core and 15 AI-specific reporting items).	Principal investigators, clinical researchers
DECIDE-AI	Guideline framework for clinical evaluations of early-stage decision support systems developed using AI (10 generic and 17 AI-specific reporting items).	Investigators, clinicians, patients, policymakers
Clinician Checklist	Describes recommendations on studies that evaluate the suitability of AI applications for clinical settings.	Clinicians
Reporting and Implementing Interventions	Describes barriers to the implementation of AI in medicine and provides solutions to address them.	Health care organizations
20 Critical Questions	Proposes 20 questions for evaluating the development and use of AI in research (20 reporting items)	Investigators, clinicians, patients, policymakers
Comprehensive Peer Review Checklist	Proposes a comprehensive checklist for the self-assessment and evaluation of medical papers (30 reporting items)	Investigators, editors and peer reviewers
PROBAST-AI and TRIPOD-AI	Guidelines on using AI/ML with sensitivity and precenting bias in data analysis and reporting	Researchers, investigators, peer reviewers
Ethical Considerations	Describes a roadmap for considering ethical aspects of AI with health care applications	AI developers, investigators, clinicians, policymakers
Users' Guide	Describes an approach for assessing published literature using AI for medical diagnoses	Clinicians
Clinical AI Research (CAIR) Checklist	Provides guidelines and an associated checklist for the reporting of AI research to clinicians (15 reporting items)	Investigators, developers, clinicians
Minimum Information on AI Reporting (MINIMAR)	Provides minimum reporting standards for AI in health care (16 reporting items)	AI developers, investigators

As per the original publications, TRIPOD-AI and PROBAST-AI guidelines aim to address the needs of prediction modelling studies from all public health domains (primary, secondary, tertiary and nursing home care) and all corresponding target populations (healthy individuals, suspected and diseased individuals)[12].

Clinical AI Research Checklist :

The Clinical AI Research (CAIR) guideline was documented to help clinicians, data collectors, and other clinical workers in assimilating, organizing, and appraising clinical tasks performed using AI. The guideline is meant for effectively supporting the use of AI in ensuring quality, maintaining timelines, streamlining data capture processes, and optimizing the precision of data collection[13].

Olczak, *et al* simplified the application of AI/ML systems with regard to classifying clinical data, image analysis, segmentation and localization, performing regression modelling, translating medical documents for wider dissemination, and clustering data for deeper analyses[13].

Additionally, Olczak, *et al* proposed the need for a guideline on managing missing data and scarcity of data, especially in handling new clinical data obtained from subjects that cannot be combined with existing data for interpretation or analysis. Next, the guideline is expected to explain how overfitting of data within models can be avoided and how model training and validations are to be performed for clinical trials. Olczak, *et al* have listed the calculation methods for assessing the consistency, accuracy, sensitivity, and optimal ML model performance[13].

Checklist for Artificial Intelligence in Medical Imaging :

The Checklist for Artificial Intelligence in Medical Imaging (CLAIM) guideline serves as a 'best practice' recommendation for reporting original work on AI-

supported medical imaging[18], providing a framework for systematic assessment of medical image analysis to peer reviewers in medicine. CLAIM has seven categories — each aspect addressing a manuscript's title, abstract, introduction, methods, results, discussion, and other parts together forming a 42-item checklist. The CLAIM guideline focuses on clear reporting of training procedures and hyperparameters to enable replicability and repeatability by other researchers.

AI Application in Clinical Decision Support Systems: DECIDE-AI Guideline :

Various AI-based clinical decision support systems have been used in preclinical, in silico, evaluation research phases, of which some have been handpicked for demonstrating benefits for patients. Although existing reporting guidelines exist for some of these study designs , none of them cover all the core aspects of AI system early-stage evaluation and none would fit all possible study designs; DECIDE-AI was therefore developed as a new independent clinical outcomes' data reporting guideline.

The DECIDE-AI statement provides a multistakeholder, consensus-based reporting guideline for the Developmental and Exploratory Clinical Investigations of DEcision support systems driven by Artificial Intelligence. The final guideline was determined at a virtual consensus meeting, and its checklist with the explanation and elaboration sections were refined based on feedback from a qualitative evaluation process.

Guidelines on Using AI for Clinical Trial Reporting: CONSORT-AI Extension and SPIRIT-AI Extension (Table 2).

The SPIRIT-AI extension includes 15 new items pertaining to clinical trial protocols of AI interventions[10], which should be routinely reported in addition to the core SPIRIT 2013 requirements. To comply with the SPIRIT-AI conventions, investigators should describe the AI intervention in articulate non-ambiguous language, including the instructions and skills required for use, the settings for integrating the novel AI intervention, considerations for the input and output data handling, human–AI interaction, and analysis of AI error cases. The SPIRIT-AI extension requires the compliance with existing SPIRIT 2013 items and additional 15 items in the trial protocols of AI interventions. It is necessary to fully describe the AI/ML intervention and specify the type of model, its intended use, version, exact algorithm necessary, and the exact role of the AI/ML for optimal results.

The SPIRIT-AI and CONSORT-AI Working Group published the CONSORT-AI extension for ensuring transparent reporting in clinical research, especially for new therapies[9,10]. The guideline is particularly meant for clinical trials evaluating interventions with an AI component[9]. It was developed in parallel with its companion statement for clinical trial protocols: SPIRIT-AI. The CONSORT-AI extension includes 14 new items relevant for AI interventions, which should be routinely reported in addition to the core

Table 2 — *Summary of existing mandatory guidelines for AI in medicine*

Name	Stage	Study design	Comment
CONSORT-AI	Comparative prospective evaluation	Randomised controlled trials*	Extension of CONSORT. Used to report randomised controlled trials evaluating AI systems as interventions (large scale, summative evaluation), independently of the AI system modality (diagnostic, prognostic, therapeutic). Focuses on effectiveness and safety
SPIRIT-AI	Comparative prospective evaluation	Randomised controlled trials (protocol)*	Extension of SPIRIT. Used to report the protocols of randomised controlled trials evaluating AI systems as interventions
DECIDE-AI	Early live clinical evaluation*	Various clinical studies (prospective cohort studies, non-randomised controlled trials, etc.) with additional features such as modification of intervention, analysis of prespecified subgroups, or learning curve analysis	Standalone guideline. Used to report the early evaluation of AI systems as an intervention in live clinical settings (small scale, formative evaluation), independently of the study design and AI system modality (diagnostic, prognostic, therapeutic). Focuses on clinical utility, safety, and human factors
TRIPOD-AI	Preclinical development	Prediction model evaluation*	Extension of TRIPOD. Used to report prediction models (diagnostic or prognostic) development, validation and updates. Focuses on model performance
STARD-AI	Preclinical development, offline validation	Diagnostic accuracy studies*	Extension of STARD. Used to report diagnostic accuracy studies, either at development stage or as an offline validation in clinical settings. Focuses on diagnostic accuracy

CONSORT 2010 items. In both CONSORT-AI and its companion project SPIRIT-AI, a major emphasis was the addition of several new items relating to the intervention itself and its application in the clinical context. Items 5(i)–(vi) were added to address AI-specific considerations when describing the intervention.

US-FDA Approach of Monitoring AI/ML Applications :

Digital health products have become a crucial field of interest for the US-FDA, especially AI. The federal agency advices that the indented use of a medical AI/ML product whether as a 'general wellness product' (consumer-grade) or as a 'medical device' (clinical-grade) needs to be determined prior to starting the marketing authorization application process[16].

Regarding AI/ML products that are listed under the Software as a Medical Device (SaMD) category, the US-FDA mandates that, if the AI/ML product is labelled, promoted, or used as per the definition of 'device' in section 201(h) of the Federal Food Drug & Cosmetic (FD & C) Act, it falls under the scope of FDA regulations as a SaMD and requires pre-marketing and post-marketing regulatory controls, including: (1) FDA establishment registration, device listing, and pre-market notification requirements (Title 21 CFR Part 807); (2) labelling requirements (Title 21 CFR Part 801 and 809.10; (3) current Good Manufacturing Practices (GMP) and quality system requirements (Title 21 CFR Part 820); and (4) medical device reporting requirements (Title 21 CFR Part 803)[17].

In the recent years, the FDA had published dedicated guidance documents on the use of AI in drug development and it recognizes its emergent role in improving the efficiency of clinical research. In its recently published 33-page guidance document, the FDA mentions that AI/ML applications are being used for individual case safety report submissions. Permissible AL/ML uses for event monitoring and recording, case validation, removing duplicate data, and quality control of MeDRA coding have been described.

Guidance from EMA for AI Use in Medicinal Product Lifecycle :

The European Medical Agency (EMA) has released draft guidelines in July, 2023, describing the length and breadth of the considerations for using AI and machine learning in every stage of medicinal product development[5], including the scientific principles for regulatory evaluation. Regarding the development lifecycles of medical devices, the EMA states that medical devices with AI/ML technology can be used for clinical development, evidence generation, and data evaluation in support of a marketing authorisation application as a sole medicinal product or as a combined (drug + device) therapy. In such cases, the EMA will assess the adequacy of device characteristics to generate evidence that supports an EU marketing authorisation and all other proposed combined uses.

EMA Guidance on Ethical Aspects and Trustworthiness on AI :

The EMA has shared fresh principles on the trustworthy use of AI tools and published the Assessment List for Trustworthy Artificial Intelligence (ALTAI) for self-assessment prepared by the independent High-Level Expert Group on AI that was established by the European Commission.[5]

The list is applicable for all bodies and includes the below 7 key aspects of ethics and safety:

(1) Human agency and oversight;

(2) Technical robustness and safety;

(3) Privacy and data governance;

(4) Transparency;

(5) Accountability;

(6) Societal and environmental well-being;

(7) Diversity, non-discrimination, and fairness.

Discussion

As of now, there is little clarity on the extent of using LLMs in clinical documentation. The draft reflection paper from the EMA does not have any directive regarding the use of chatbots or generative AI in medical writing.

Using LLM Chatbots in Medical Writing :

There has been increased curiosity and criticism in the aspect of using chatbots to compile medical documents. Ever since OpenAI launched ChatGPT in January, 2023, several researchers and medical writers conducted trial runs of retrieving information using this user-friendly chatbot[18]. Initially, as reported

by Salvagno, *et al*, the results and responses from the chatbot were factually incorrect; some attempts provided older information, hinting at the limited data fed into the databank that the chatbot depended on[19,20]. This sparked both more interest and massive scrutiny among members of the medical fraternity, as more trial runs led to the accumulation of readable, but not appreciable medical information.

Recently, the role of an AI chatbot in medical writing was fragmented to provide a refined understanding of the quality of the content generated by ChatGPT-4 depends largely on the prompts given by the user – thus enabling the dawn of a new domain called as "prompt engineering". Until now, some researchers have used ChatGPT versions and published the experiences of routine medical writing activities such as rewording sentences and paraphrasing, summarizing, copyediting, writing methods section, tabulating content, creating Abstracts, reference management, and complete tasks such as creating patient-facing medical content, suggesting peer reviewers, writing grants, recognizing research ideas, and finding gaps in literature, offering potentially useful manuscript titles and generating short titles.

Response from the ICJME :

The International Committee of Medical Journal Editors (ICJME) specifies that ChatGPT cannot be listed as an author in any ICJME-accredited journal. Moreover, it is mandatory to disclose the use of other AI tools including ML algorithms, LLMs, etc, in the preparation of study documents and medical publication materials, including the shorter content pieces facing patients. The exact details of the use of AI tools must be provided in the Disclosure section of the manuscript as well as the cover letter. The ICJME emphasized on the resounding principles of accountability, integrity, and originality of work and instructs that "Authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased."

Ethical Concerns with the Use of LLMs in Medical Documentation :

Beyond the misleading and unreadable text generation outputs, the need for assimilating information and feeding it into the LLM for appropriate output has been concerned with data breaches and unwarranted dissemination. There is also a risk of increasing the bias in research and publication. While clinicians can benefit from the text generation and summarization capabilities of AI chatbots, a word of caution and an eagle's eye on the data fed to the LLM is necessary to determine the correctness of the output...

Conclusion

Given that AI and its application in the healthcare industry are here to stay, medical writers need to arm up with a strong AI portfolio. With the regulatory oversight on medical AI increasing every day and achieving an encapsulated structure, it is imperative for medical writers to address the enormity of data. While the AI invasion is still a matter of debate, medical writers using AI are mandated to uphold the principles of transparency, inclusion, accountability, trust, and patient safety in all processes of the drug and medical device development lifecycle and design the routine SOPs as per the EMA and FDA directives on AI use in clinical and scientific documentation. Furthermore, publication writers are expected to brace up on the updated recommendations by the EQUATOR NETWORK and ICJME to ensure integrity and credibility of their scientific materials.

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Case Series

Uncommon Phenotypes of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease : A Case Series

Rajarshi Chakraborty[1], Rajesh Verma[2], Harish Nigam[3], Ankit Khetan[3]

Abstract

Background : Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) is a primary demyelinating autoimmune disorder of the Central Nervous System targeting the myelin. In recent time, the incidence and diversity of MOGAD cases are increasing. This may open-up further clinical presentations of MOGAD and there is requirement for enhancing its awareness for further detection. In this case series, we discuss seven distinct uncommon clinical phenotypes with radiological interpretation observed in MOGAD.

Key words : MOGAD, Phenotype, Uncommon.

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease(MOGAD) is an autoimmune primary demyelinating disorder of the Central Nervous System (CNS). Forty five years from its inception in experimental encephalomyelitis, dating back to 1980s, it has shown a variety of clinico-radiological presentations worldwide[1]. Nonetheless, its incidence and importance is increasing in the Asian population. Neuromyelitis Optica Spectrum Disease (NMOSD), Multiple Sclerosis (MS), Vasculitis and infections of the CNS are important differentials. A multitude of case studies and case reports have been documented in MOGAD. This case series tries to explore the uncommon phenotypes of MOGAD along with discussing such phenomena (Table 1, Figs 1 and 2 as per case description). This case-series comprises of 7 MOGAD cases selected out of 25 MOGAD cases, being admitted in neurology department over a-2-years-period.

Editor's Comment :

- Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) is a newer demyelinating entity of the central nervous system.
- The spectrum of clinical and imaging features are expanding with time.
- Clinicians should have a broader approach in suspecting MOGAD in different clinical phenotypes.

Case 1 :

A 25-year-old-male presented with complaints of bilateral vision loss for 4 days followed by paraplegia with bowel/bladder involvement. He was conscious and oriented to time, place and person. Pupil were bilateral sluggishly reactive to light. His visual acuity was Finger Counting (FC) at ½ metre bilaterally with normal extra-ocular movements. He had Upper Motor Neuron (UMN) paraparesis. Magnetic Resonance Imaging (MRI) showed cerebritis, bilateral Optic Neuritis (ON) with chiasmal lesions and Longitudinally Extensive Transverse Myelitis (LETM). His serum Anti-MOG Antibody (Ab) was positive, while Anti-AQP4 (aquaporin-4) Ab and Cerebrospinal Fluid (CSF) Oligoclonal Band (OCB) were negative. He was managed with pulse-dose methyl-prednisolone, followed by prednisolone. At 3-months, complete recovery occurred in vision and lower-limb power.

Case 2 :

A 17-year-old-male presented with fever followed by weakness of all four limbs with bowel/bladder incontinence, dysphagia and dysarthria for 5 days. He was conscious and oriented. His ophthalmic examination were normal. He had UMN quadriparesis with bulbar palsy. His MRI showed cervico-dorsal LETM(C3-D5), features of Acute Disseminated Encephalomyelitis (ADEM), corpus callosal and brainstem lesions. His Anti-MOG-Ab was positive, Anti-AQP4 and CSF-OCB were negative. He was managed with steroids (pulse-dose methyl-prednisolone, followed by prednisolone) and showed complete recovery at 3 months.

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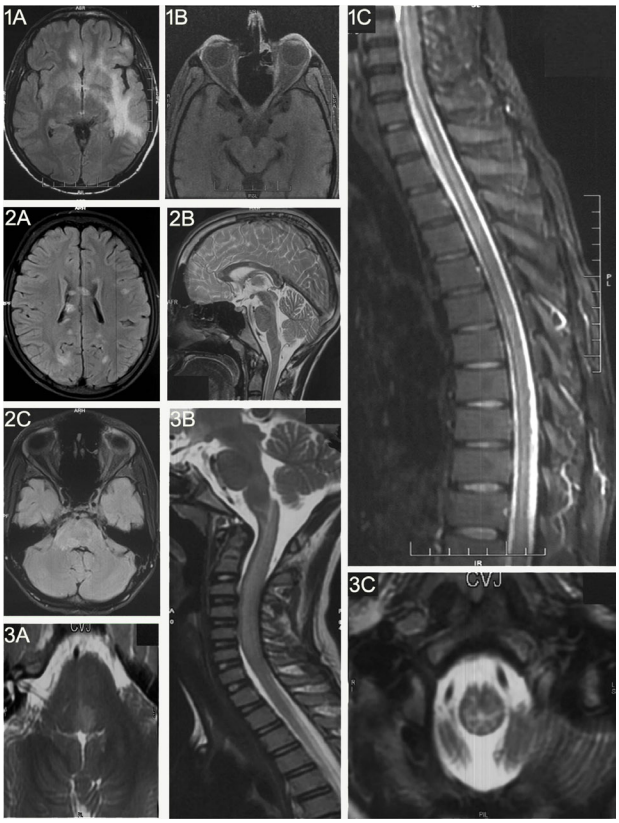

Fig 1 — Brain Magnetic Resonance Imaging(MRI) showing asymmetric left-temporal cerebritis (1A); longitudinally extensive optic neuritis(LEON) with chiasmal lesion(1B); longitudinally extensive transverse myelitis(LETM)(1C); pericallosal and juxtacortical hyperintensity (2A); multiple ovoid callosal T2 hyperintensities(2B); Middle Cerebellar Peduncle (MCP) sign (2C) and dorsal-medullary hyperintensity (area postrema involvement) (3A); LETM extending upto medulla (3B); moth-eaten appearance of cervical cord (3C).

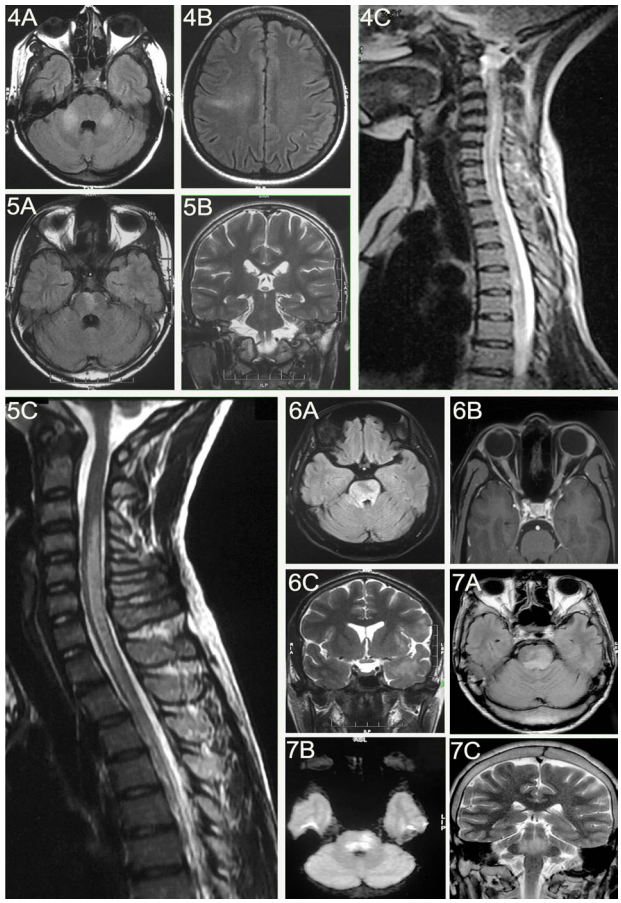

Fig 2 — MRI-brain showing bilateral MCP sign(4A) and right fronto-parietal cerebritis (4B); LETM (4C); medial longitudinal fasciculus hyperintensity (5A); central pontine hyperintensity (5B); LETM (5C); pontine hyperintensity with bilateral MCP sign(6A); contrast-enhancement of bilateral optic nerves (6B); optic chiasmal hyperintensity (6C); pontine hyperintensities(7A), with diffusion restriction (7B) and coronal-T2 ponto-cerebellar hyperintensity (rhombencephalitis)(7C).

Case 3 :

A 10-year-old-male presented with intractable vomiting for 4 days followed by bilateral lower limb weakness with bowel/bladder incontinence for 2 days. His vision was normal. He had UMN paraparesis with normal eye examination. MRI showed area postrema lesion, with LETM (cervico-medullary junction/CMJ to C7) showing moth-eaten appearance. His Anti-AQP4-Ab and CSF-OCB were negative, but Anti-MOG-Ab was positive. He was managed with steroids (pulse-dose methyl-prednisolone, followed by prednisolone) and showed complete recovery at 3-months.

Case 4 :

A 35-year-old-female presented with acute-onset weakness of all four limbs with bowel/bladder incontinence. Her examination showed UMN quadriplegia Her MRI showed LETM (cervico-medullary junction to conus medullaris), bilateral Middle Cerebellar Peduncle (MCP) sign and cerebritis. Her Anti-MOG Ab was positive, while His Anti-AQP4 Ab and CSF-OCB were negative. She was started on pulse methylprednisolone, followed by Intravenous Immunoglobulin (IVIg), without improvement. Rituximab therapy was also tried, but there was poor recovery at 3-months.

Case 5 :

A 17-year-old-male presented with high-grade fever 3 days back, followed by weakness of all four limbs, along with bladder/bowel involvement. His ophthalmic examination was normal except for having adduction lag in left eye and abducting eye nystagmus in right

Table 1 — *Uncommon phenotypes of MOGAD patients*

Age (Y), Sex	Clinical presentation	Magnetic resonance imaging			Treatment	Follow-up
		Brain	Orbit	Spine		
25, M	Bilateral vision loss and paraparesis for 4 days	Cerebritis	B/L ON and chiasmal lesion	D6-D12 LETM	MPS, f/b prednisolone	At 3 months, complete recovery in vision and lower limb power.
17, M	Quadriparesis and bulbar palsy for 5 days	ADEM with corpus callosum and brainstem lesions	Normal	C3-D5 LETM	MPS, f/b prednisolone	At 3 months, complete recovery
10, M	Intractable vomiting, paraparesis for 4 days	Area postrema lesion	Normal	Cervico-medullary Junction to C7 LETM, moth-eaten appearance	MPS, f/b prednisolone	At 3 months, complete recovery
35, F	Quadriparesis for 2 days	B/L MCP sign, cerebritis	Normal	Cervico-medullary Junction to conus medullaris	MPS, IVIg, RTX	Poor recovery at 3 months
17, M	Quadriparesis, INO for 3 days	MLF lesion	Normal	C3-D11 LETM	MPS, f/b prednisolone	At 3 months, complete recovery
30, F	B/L vision loss, ataxia, right-sided hemiparesis for 10 days	B/L MCP sign and pontine lesion	B/L ON and chiasmal lesion	Normal	MPS, IVIg, RTX	Poor recovery, remained blind at 3 months
36, M	Fever, tinnitus, right-sided hemiparesis, dysphagia, dysarthria, horizontal gaze palsy	Flluffy pontine lesion	Normal	Normal	MPS, f/b prednisolone	At 1 month, complete recovery

Note : Y=Years; M=Male; F=Female; B/L=Bilateral; On=Optic Neuritis; D=Dorsal, C=Cervical; Letm=Longitudinally Extensive Transverse Myelitis; MPS=Methyl Prednisolone; ADEM=Acute Disseminated Encephalomyelitis; f/b=followed by; MCP=Middle Cerebellar Peduncle Sign; IVIg=Intravenous Immunoglobulin, RTX=Rituximab; INO=Internuclear Ophthalmoplegia; MLF=Medial Longitudinal Fasciculus

eye on right gaze. He has UMN quadriplegia. His MRI showed LETM(C3-D11) along-with Medial Longitudinal Fasciculus (MLF) lesion. His Anti-AQP4 Ab and CSF-OCB were negative, but Anti-MOG Ab was positive. He was managed with steroids (pulse-dose methyl-prednisolone, followed by prednisolone) and showed complete recovery at 3-months

Case 6 :

A 30-year-female presented with acute-onset bilateral vision loss, headache, painful ocular movements, ataxia and right-sided weakness over 10 days. She had history of vision loss in left eye 1 year back which recovered completely with treatment. At present, her visual acuity was FC at 1 metre in right eye and 6/60 in left eye. Pupils were mid-dilated and sluggishly reactive to light. She had ataxia, cerebellar signs along with UMN right-sided hemiplegia. MRI showed bilateral ON with chiasmal lesion, pontine lesions and Bilateral MCP sign. Anti-AQP4-Ab and CSF-OCB were negative, while Anti-MOG-Ab was positive. She was treated with pulse methyl-prednisolone, IVIg and Rituximab therapy. Her ataxia and hemiplegia improved but her vision didn't show any improvement.

Case 7 :

A 36-year-old-male presented with fever of 3 days duration followed by tinnitus in the right ear, right-sided weakness of body including face. It was followed by diplopia, dysarthria and dysphagia. Examination revealed right-sided UMN type complete hemiplegia, horizontal gaze palsy with bulbar palsy. Patient also had reduced sensation over right half of face with reduced movements of sight side of palate. MRI revealed fluffy hyperintense pontine signals. A diagnosis of acute rhombencephalitis was made on the basis of clinical and radiological findings and patient was managed with intravenous pulse steroid therapy. Patient improved drastically over 1-month.

Discussion

MOGAD is an antibody-mediated inflammatory disorder of CNS myelin at the outermost myelin sheath layers and oligodendrocyte cell surface myelin, and hence can have features common to NMOSD and MS[2]. MOGAD usually affects the anterior part of optic nerves, lobes, deep gray matter, and spinal cord. In this case series, we tried to describe the different

aspects of MOGAD manifestation with review of literature.

Chiasmal involvement has been observed in only 5-12% MOGAD cases in a study by Ramanathan et al. and Chen, *et al*[3,4]. Asymptomatic Corpus Callosal (CC) involvement is observed in18-33% of MOGAD[5]. In a study by Chia, *et al*, CC lesions were variable, often large and involving the sagittal midline, with frequent extra-callosal extension to bilateral sagittal frontoparietal cortices in MOGAD[6]. Area Postrema Syndrome is characterized by Intractable Nausea, Vomiting and Hiccups (INVH) for ≥48 hours and can occur in isolation with discrete T2/FLAIR and T1-gadolinium-enhancing lesions involving the area postrema[7]. Till date, APS is recognized in only one MOGAD patient, with isolated INVH in a study with an incidence of 0.6%[8]. It may be due to disruption of the "emesis circuit" between the area postrema, nucleus tractus solitarius, and the central pattern generator. INO is rarely described in MOGAD with isolated anecdotal cases observed Globally[9]. In a case report, new-onset INO was observed in the background of recurrent LETM due to MOGAD despite on immune therapy[10]. Bulbar palsy is another rare entity observed in MOGAD with anecdotal case reports[11,12]. Patients with brainstem involvement account for 30% MOGAD-associated encephalomyelitis cases and isolated brainstem encephalitis that occurs without ON or myelitis is much rarer, accounting for only 1.8%[13].

In this case series, we highlight the atypical clinico-radiological presentations of MOGAD. This is the first case series of MOGAD targeted to uncommon patterns of Central Nervous System involvement.

Conclusion

MOGAD can have a plethora of neurological manifestation, similar to MS and NMOSD requiring clinical acumen. There is an inevitable requirement for enhancing the awareness about such atypical case presentations.

Declaration of patient consent :

The authors certify that they have obtained all appropriate patient consent forms for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest : None.

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Case Report

Obstetrician's Distress in an Unusually Delayed Vaginal Delivery of Second Twin : A Case Report

Shilpa Kshirsagar[1], Prachi Dwivedi[2], Charmy Vashi[3], Shankar Burute[4]

Abstract

Background : We report a case of vaginal delivery of both twins with a delay of almost an hour after the first twin delivery of a woman in her 20s with second gravida abortion one at 38 weeks gestational age. The case was of a dichorionic diamniotic twins with labour pains in a case of infertility conceived with ovulation induction. Patient had uneventful antenatal period and presented to labour room in latent labour with first fetus in cephalic presentation and second with breech. Labour was augmented with oxytocin and vaginal delivery was achieved successfully for the first female baby with a birth weight of 2.70 kg and APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score of 9/10. After delivery of the first twin, adequate contractions were not achieved even after the maximal dose of oxytocin infusion (8 units in 500 mL Ringer's lactate solution at 60 dpm). ARM was done at very high station keeping everything ready for emergency LSCS. Continuous monitoring of fetal heart rate and vital parameters of mother was performed with utmost patience expecting vaginal delivery. A healthy male child of 3.0 kg was delivered vaginally in vertex presentation after more than an hour of the first twin with an APGAR score of 8/10. The mother was shifted to the ward and both babies on the mother's side was the happy end of our battle.

Key words : Twins, Vaginal Delivery, ARM, Oxytocin, APGAR Score.

In India, the reported incidence of twins was found to be 30.5 per 1000 deliveries and this is due to the use of assisted reproductive techniques and pregnancy at advanced age[1].

Due to a lack of prospective studies to choose the best mode of delivery on the basis of individual case characteristics, on one hand, expertise in the management of vaginal twin delivery is mandatory and on the other hand some obstetricians prefer caesarean section delivery for good perinatal outcomes in twin pregnancies at ≥36 weeks gestation.[2]

Herein we aimed to report a case of vaginal delivery of healthy twins with a delay of more than an hour in delivery of second twin after the first twin delivery at term which is a rare event.

Case Report

It's a case of registered second gravida with previous one abortion at 38 weeks of gestational age with dichorionic diamniotic twins. She presented to us in latent labour. She had conceived after ovulation induction done for 4 years infertility. Her antenatal period was uneventful and latest ultrasound examination done at 35 weeks of pregnancy revealed she was having two foetuses of average gestational age of 35 weeks with adequate liquor. She was admitted and CTGs of both foetuses were reactive, hence proceeded with vaginal trial with necessary consents. Labour was augmented with ARM followed by oxytocin in view of slow progress noted by plotting partograph. On full dilataion, patient was shifted to the OT for further smooth management considering breech presentation of second twin. Vigilant monitoring of the patient's pulse rate, contractions and continuous fetal heart rate monitoring by Cardiotocography (CTG) was done. A healthy female child of 2.70 kg was delivered vaginally in vertex presentation at 11:28 PM. The baby cried immediately after birth with an APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score of 9/10.

After delivery of the first twin, the lie was kept stable abdominally, longitudinally, and fetus was noted in vertex presentation. The cervix was 7-8 cm dilated with high station and no contractions. Labour augmentation was continued with oxytocin infusion. However, at a maximal dose (8 units in 500 mL Ringer's lactate solution at 60 dpm) adequate contractions could not be achieved. Continuous monitoring of fetal heart rate and patient's vitals was done. Decision for ARM was made as oxytocin

Editor's Comment :

- Do not rush for cesarean, if second twin takes more time to deliver.
- If found clinically normal, outcome will be good even in delayed vaginal delivery.

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could not give optimum results in augmenting contractions. Controlled ARM was done keeping everything ready for emergency LSCS, clear liquor was drained. Eventually after ARM, uterine contractions started and also response to oxytocin infusion was noted. A healthy male child of 3 kg was delivered in vertex presentation at 12:33 AM almost an hour after delivery of the first twin. The baby cried immediately after birth, and the APGAR score was 8/10.

The placenta and membranes were delivered spontaneously and completely. Episiotomy sutured in all layers; haemostasis achieved. No tear and no postpartum haemorrhage was noted. The patient was shifted to the ward with both babies' mother's side.

Discussion

The findings from this case study depicted that the second twin weighing 3.0 kg was delivered successfully vaginally after a delay of more than an hour after the delivery of the first twin with an APGAR score of 8/10. Generally, planned caesarean section delivery is recommended in twin pregnancy, when the pregnancy is an assisted one and the woman aged greater than 40 years[3,4]. Furthermore, Dong *et al.,* with a large sample size reported that planned caesarean section lowers the risk of serious neonatal morbidity, in particular of the second twin. Notably, it favours planned caesarean at gestational week ≥36[2].

Contradictorily some clinicians expressed that the decision on the mode of delivery should be made on the basis of the comprehensive condition of the mother, rather than being biased by the fact that the pregnancy is a precious one. A commonly accepted view is that the interval between the birth of the first and second twins should be preferably within 15 minutes and certainly not more than 30 minutes.[5] In contrast with literature findings, in our case study, a successful vaginal delivery was achieved almost after an hour after the first twin delivery alongside continuous monitoring of the fetal heart rate and vital parameters of the mother. Rayburn *et al* revealed that if there is continuous fetal and uterine monitoring, a time restriction for the delivery interval between the first and second infants is not necessary[6]. As per Stein *et al,* some of the factors responsible for a longer twin-to-twin delivery time interval are as follows; breech, transverse lie, birth weight discordance with the second twin at least 20% larger, fetal distress, and vaginal operative delivery[7]. Lindross *et al,* demonstrated in their study that an association, but not necessarily a causality, between twin-to-twin delivery interval and composite outcome of metabolic acidosis was seen[8].

Conclusion

The second twin delivery was successfully achieved through vaginal delivery after an hour after the first twin delivery providing continuous monitoring of the fetal heart rate and vital parameters of the mother. When all the parameters are normal, we still recommend to go ahead with vaginal trial since twin pregnancy and delay of second twin ≥30 mins are not always indications for caesarean section.

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Letters to the Editor

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

Minocycline for Rosacea : Balancing Efficacy with Safety — Advancing Treatment through Innovation and Vigilance

Sir, — Rosacea is a chronic inflammatory skin condition that affects millions of adults worldwide, characterized by erythema, telangiectasia, and inflammatory lesions. Despite its prevalence, effective long-term management remains a challenge due to the complex pathophysiology of the disease. The recent advancements in therapeutic options, particularly the FDA approval of oral minocycline for inflammatory lesions, mark a significant milestone in addressing these challenges. This editorial examines the evolution of minocycline's role in rosacea management, with a focus on its efficacy, safety profile, and the potential for new formulations to improve patient outcomes.

Efficacy of Minocycline in Rosacea :

In 2020, minocycline was approved by the FDA as an oral therapy specifically targeting inflammatory lesions in adult rosacea patients[1]. This approval was supported by robust clinical trials demonstrating its efficacy in reducing lesion counts and enhancing patient-reported quality of life metrics. For example, phase III trials showed that low-dose, extended-release minocycline significantly reduced inflammatory lesions as early as four weeks into treatment, with further improvement observed through week 12. Importantly, these results underscore the anti-inflammatory properties of minocycline, which act by modulating key inflammatory pathways implicated in rosacea rather than solely addressing bacterial activity[2].

Patients receiving minocycline also reported relief from hallmark symptoms of rosacea, such as redness, swelling, and burning sensations. These outcomes emphasize the drug's role as an effective treatment option, particularly for moderate-to-severe cases where topical treatments may fall short. The extended-release formulation not only enhances therapeutic efficacy but also minimizes fluctuations in drug levels, reducing the likelihood of adverse reactions commonly associated with traditional formulations[3].

Comparative Efficacy and Emerging Role :

When compared to existing treatments such as topical metronidazole, azelaic acid, and other oral antibiotics like doxycycline, minocycline offers several distinct advantages. Its anti-inflammatory mechanism is more targeted, resulting in broader applicability for patients resistant to other therapies. Furthermore, clinical evidence suggests that minocycline achieves comparable or superior efficacy while offering the convenience of once-daily dosing[4].

This positions minocycline as an attractive option in the therapeutic arsenal for rosacea, addressing a critical need for treatments that balance efficacy and patient adherence. Notably, the approval of Emrosii (minocycline hydrochloride) in November 2024 as a next-generation extended-release capsule reflects ongoing efforts to refine the drug's safety and tolerability[5].

Safety Concerns and Drug Monitoring :

Despite its efficacy, the safety profile of minocycline necessitates vigilance, particularly for long-term use. Common Adverse Drug Reactions (ADRs) include gastrointestinal disturbances, dizziness and photosensitivity. Rare but serious effects such as drug-induced lupus, liver toxicity, and skin pigmentation have also been documented[6].

To mitigate these risks, clinicians must adopt a proactive approach to drug monitoring. Regular assessment of liver and renal function, especially for patients on prolonged therapy, is essential. Moreover, patient education on recognizing early signs of ADRs plays a crucial role in preventing complications. Tailored dosing strategies, such as initiating treatment at lower doses and escalating only as needed, can further enhance safety[7].

Certain populations, such as individuals with pre-existing liver or renal impairments, pregnant patients, and those taking concurrent hepatotoxic medications, may require additional precautions. Identifying and addressing these risk factors is critical to optimizing therapeutic outcomes while minimizing harm[8].

Balancing Efficacy and Safety in Clinical Practice :

Effective rosacea management involves striking a balance between maximizing therapeutic benefits and minimizing risks. For clinicians, this requires a nuanced approach that integrates evidence-based protocols with individualized patient care. Factors such as disease severity, patient preferences, and comorbidities must be carefully weighed when selecting minocycline or any other treatment option[9].

Preventive measures to mitigate ADRs include :

(1) Regular monitoring of organ function.

(2) Educating patients on recognizing symptoms like unusual skin discoloration or persistent nausea.

(3) Considering alternative therapies for high-risk patients.

By fostering open communication and encouraging adherence to monitoring protocols, healthcare providers can enhance the overall safety and efficacy of minocycline therapy.

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Future Directions :

The approval of Emrosi underscores the potential for innovation in minocycline formulations to address unmet needs in rosacea treatment. Future research should prioritize:

(1) Long-term Safety Studies: To better understand the implications of extended minocycline use in diverse patient populations.

(2) Alternative Formulations: Exploring topical or even non-antibiotic derivatives to reduce systemic ADRs.

(3) Mechanistic Insights: Elucidating the anti-inflammatory pathways modulated by minocycline to inform the development of next-generation therapies[10].

As the landscape of rosacea management evolves, ongoing collaboration between clinicians, researchers, and regulatory bodies will be crucial to ensuring that advancements in therapy translate into meaningful improvements in patient care.

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Controlled Molecular Engineering in T2DM (Possible future directions)

Sir, — With the given clinical protocol of repeat Blood Glucose estimations at regular intervals along with interpretation of repeat values of Hemoglobin Glycation (HBA1c) do give reasonable indications in clinical diagnostics. But definite *Prognostic and Predictive Diagnostics* however is still in early stages of development[1].

Question that remains:

HBA1c — Is it a comprehensive parameter for both Diagnosis as well as Prognosis (walk of the disease), or a half-done analyte we are happy with?

Looks like it's time this question should be raised for better following of the disease with one or more direct indicator(s) of ischemia being brought into consideration rather than simply following prevailing five types of blood glucose values at a given time as indirect presumptive indicators !

HBA1c, molecularly depicts level of non-enzymatic glycation of hemoglobin, a flowing phase protein, which gets anyway eliminated from system every 100 days +/-. This value is a glycemic indicator rather than depicting any irreversible Ischemic damage done by the C-6 carbohydrate.

T2DM damages are mostly concentrated in exchange bed capillaries in all organs where size of capillaries varies between 0.2 to 10 micro-meters. While entire human system has this exchange bed capillaries, maximal clinical expressions come from kidney,eye,brain,heart, skin and peripheral vessels.

Molecular basis of these damages, collectively called — Vasculitis — are as follows:

Glucose exists in two forms :

@ alpha-d-glucose

@ beta-d-glucose

And as their racemic mixture.

Both alpha- and beta-forms are closed ring forms with a few exposed least reactive hydroxyl groups (Fig 1). Oral carbohydrate consumption leads to a buildup of blood level of these two forms, finally settling to a mixed form mentioned.This interchange takes place within aqueous phase of blood where alpha-d-form muta-rotates to the beta-d-form and vice-versa finally settling to a racemic mix of the two. The process, as mentioned, is known as mutarotation.

What is extremely important is the fact that the bidirectional transformation passes through an open-chain form of glucose molecule for an extremely tiny fraction of a second with a hyper-reactive aldehyde group getting exposed (possibly this transition takes place in a time frame of pico-second or even less).

This super-fast hydrated-aldehyde is the central offending group of Glucose which reacts with nearly anything and everything in both *flowing phase* and *fixed phase* of blood, of which our clinical measurements, till date, have remained confined to Hemoglobin Glycation only, a flowing phase phenomenon !

Given this molecular transformation as background, important question that arises is as follows :

Do we need a new *prognostic parameter*?

Perhaps yes.

HBA1c is a globally accepted diagnostic indicator, but it hardly tells anything about the molecular pathology of vascular occlusion and resulting immunological reactions — collectively known clinically as Vasculitis.

Essentially Stage - I damage in T2DM is nothing but caused by the open-frame glucose molecule in muta-rotation with generated hyper-transient-hyper-reactive -CHO group getting adhered to the fixed phase exposed reactive groups (-NH_2, -COOH, -OH and -C=O) on the surface of endothelial cells in micro-capillaries across the organs, in addition to forming AGEs.

Deficiency in our ways of looking at T2DM lies in:

@ following the offending agent,glucose, in various forms only,

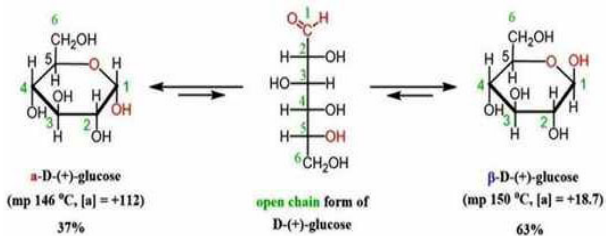

Fig 1 — Schematic presentation of mutarotation, a textbook material

@ our efforts of having peripheral and indirect assessment of progress of the disease (prognosis) from glycation of a flowing phase protein, Hb, whereas till date there is no stable reproducible parameter of individual organ and or system ischemia which is the core of Diabetic molecular pathology.

To have a more comprehensive assessment of disease progress, we should have more direct assessment parameter(s)–like *differential organ specific and collective ischemia indicators* caused till date by the pico-second-nonspecific-nonenzymatic-glycation mediated by the hyper-transient aldehyde group (of 10^{-12} to 10^{-11}sec lifespan).

Needless to mention here that glycation is an irreversible process, essentially meaning — once glycosylated the adherent glucose cannot be removed. Hence, our knowledge of *Fixed Phase Glycation* (wall glycation) is of utmost importance given that the glycated wall proteins cannot be cleaned or the accumulated carbohydrate loci on micro-vascular wall cannot be removed physically in micro-exchange-beds and filter-beds, however reduction in glucose load might be achieved through Continuous Blood Glucose (CBG) monitoring and subsequent intense therapy ! And these wall accumulations in bends and corners of micro-vascular beds become secondary adherence concentrators and attachment points for activated platelets, other glycated proteins, cells with wall glycation loads, all forms of lipids and lipid-protein complexes finally resulting in fixed occlusive and flow restricting areas (points of augmented atheromatous plaque formation).

Hypertension adds to the wall injury because of high shear on capillary endothelium resulting in pre-formation of wall attachment sites for activated glucose (with active aldehyde) and other molecular invitees .

Possible Directions

(1) Inhibition or time-bound suppression of free aldehyde formation through time-controlled systemic alkalinization (pH 7.35 raised to pH 8.0).

Work is in progress for optimization of :

a) use of commercially available alkali water,

b) estimating duration of elevated pH holding vis-à-vis blood glucose levels,

c) initiation of any other adverse effect(s) in patient groups with and/or without oral hypoglycemic/insulin therapy in fresh (<2 years) and standing diabetic cases (>2 years) under active therapy and without diabetic complications (unpublished work).

While attention got focused on degree of angular shift of polarized light, the point of equilibrium, equilibrium composition and details of bond chemistry the biological importance of the hyper-transient intermediate straight molecule got to the backbench of consideration. While mutarotation is a physical phenomenon of any optically active molecule, it acquires a profound significance in case of C-6 hexose Glucose because of the in-between hyper-reactive hyper-transient aldehyde (of 10^{-12} sec +/- duration). While alpha-D and beta-D forms are nearly non-reactive from glycation point, generated aldehyde (-CHO) is a highly reactive group reacting with all other reactive groups mentioned above.

While clinical evaluation of glycation is done only in mobile-phase intra-RBC protein Hemoglobin, ideal assessment of glycation should be in both @ flow-phase and @ fixed phase proteins to

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have a comprehensive assessment of both @ glycation induced incapacitation of intra-cellular, cells-surface and free flowing proteins and @ degree of ischemia building up because of irreversibility of wall-glycation process.

Alkaline pH profoundly reduces half-life of aldehyde group because in alkaline pH aldehyde reacts with hydroxide ion leading to formation of stable end products (germinal diol or enolate ion). Alkaline pH also stabilizes glucose in its cyclic form thereby inhibiting aldehyde generation by slowing down mutarotation. *Pre and Post-meal-controlled-alkalinization* through optimized volume of alkali water possibly buys time for blood level of free glucose to get transported to intra-cellular compartment. While all other therapeutic approaches and molecules remain in play this new molecular engineering adds up in reducing extra-cellular glucose derived aldehyde and its free play in irreversible glycation of micro-capillary fixed phase proteins.

A couple of other small molecular agents – Carnosine and Lysine – to mention a couple are under active studies and screening (unpublished data)

(2) Use of conventional therapy: All forms of conventional therapeutic modes – Small molecules, Protein, Peptide(s), Fibers, Residual and Controlled Carbohydrate Diets will add-up significant value to this molecular modification approach which basically intends to reduce –CHO group generation, wall adherence of glucose and building up of *irreversible ischemia* resulting from *flow-hindrance and diffusion hindrance*.

(3) To look for reproducible robust indicator(s)of *accumulating ischemia* for objective in-therapy prognostic evaluation. Built-up-irreversible-ischemia at a given point remains completely out-of-sight of clinical considerations –now— despite very controlled glucose load achieved through rigorous therapeutic regimes. Ideal therapeutic screen at any given point must have close control of @ dynamic glucose load and @ ischemic load at that point.

(4) Induction of controlled angiogenic response – A possible new complimentary mode of therapy : Glycation being irreversible, mobile phase glycation and fixed phase glycation have different endpoints. While mobile phase glycation – HBA1c, AGEs and glycated cells are removed from circulation continuously as a function of time , fixed phase glycations – mostly endothelial surface glycation in exchange and filter beds need special attention :

@ to be either cleaned or, @ to be replaced (In-situ repair).

While in-situ cleaning is not in focus globally, in-situ replacement of capillary exchange beds, with prospect of controlled induction of controlled angiogenic response in ischemic tissues possibly constitute the final frontier[2-9]. Encouraging results obtained thus far may hold a true promise in in-situ repair of ischemic tissues and organs through a set of Low-Mol-Wt angiogen(s) with a new therapeutic direction – Controlled Reperfusionof Ischemic Tissues Through Low-Mol-Wt-Angiogenic(s), both being globally new directions. Further molecular and clinical consolidations are obvious next steps.

Conclusion

(1) T2DM now is possibly looked at partially through estimations of offending agent in different formats.

(2) Best glycation parameter depended on now, HbA1c, indicates degree of flowing-phase-glycation (glycemic index and is not an ischemic indicator).

(3) No fixed-phase-glycation data is available now.

(4) Irreversible accumulating exchange-and-filter-bed ischemia from fixed-phase-glycation constitutes the core of molecular pathology, which is not looked at by a long margin. Reduction and Control of blood glucose to a permissible level donot address past glycations resulting in summated ischemia – both systemic and organ specific. Not all diabetics are equal and uniform glycators. Different wall glycation loads and different anatomical locations at advancing stages of T2DM act as variable degrees of *Ischemia Concentrators* and *Flow Hindrancers* (Wall glycation coupled with Flow glycation – in combination – induce both flow-hindrance as well as diffusion-hindrance).

(5) Preferential organ damage, if any, like kidney versus eye, should have definite indicator(s), marker(s) — analyte or genetic .

(6) T2DM is an ischemic disease and must have ischemia diagnostics and Ischemia therapeutics.

(7) Predictive diagnostics – overall – are at preliminary stages although organ specific prediction possibility holds good prospect.

(8) Controlled Reperfusion of Ischemic Organs and Tissues particularly of T2DM origin is a clear possibility with initial technology-demonstration-studies have already proven promising – in in-vitro cell culture, in small animals and in human study. More organized broad based studies needed.

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