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Exploring New Frontiers in Medical Sciences: A Paradigm Shift in Healthcare

Medical science, the ever-evolving tapestry of human ingenuity woven against the complexities of our biology, stands at a pivotal juncture. We've conquered infectious diseases, unravelled genetic mysteries, and crafted prosthetics that mimic nature's marvels. Yet, the horizon beckons, painted with tantalizing possibilities and challenges that demand daring exploration.

In the ever-evolving landscape of medical sciences, the quest for new frontiers has been relentless. The pursuit of knowledge and innovation in this field has not only expanded our understanding of the human body but has also opened up exciting possibilities for diagnosis, treatment, and prevention of diseases.

First on the horizon is the battle against aging. For millennia, human life has bowed to the inevitable tyranny of time. But advancements in epigenetics, cellular senescence research, and regenerative medicine are chipping away at this biological barrier. Imagine a future where senescent cells, the weathered veterans of our cellular army, can be rejuvenated or eliminated, extending our healthy lifespan. Personalized gene editing technologies now hold the potential to fine-tune the very code of life, correcting debilitating genetic mutations and offering hope for previously untreatable diseases.

The landscape of infectious diseases is also being reshaped. Precision medicine, tailored to individual microbial variations, paves the way for personalized antibiotics and targeted therapies. The rise of "phages," virus-killing bacteria, and the ongoing hunt for universal vaccines offer glimpses into a future where pandemics no longer hold humanity hostage.

But it's not just conquering diseases; enlightening our understanding of the human body is equally crucial. Brain-computer interfaces promise to bridge the gap between thought and action, opening doors for neurological rehabilitation and revolutionizing our interaction with technology. Artificial intelligence is learning to analyze medical data with a superhuman eye, aiding in early diagnosis and personalized treatment plans. The burgeoning field of microbiome research is unravelling the complex interplay between our internal ecosystem of microbes and our health, promising breakthroughs in gut-brain-axis disorders and immune resilience.

The field of medical sciences is undergoing a profound transformation, propelled by groundbreaking discoveries and innovative technologies. In recent years, researchers and healthcare professionals have ventured into new frontiers, pushing the boundaries of what was once deemed impossible. The remarkable developments in medical sciences are having a transformative impact on healthcare and the potential they hold for the future.

1. Precision Medicine: Tailoring Treatment for Individuals

One of the most significant strides in medical sciences is the advent of precision medicine. Unlike traditional one-size-fits-all approaches, precision medicine tailors treatment strategies based on an individual's genetic makeup, lifestyle, and environmental factors. This approach allows for more accurate diagnoses and personalized treatment plans, minimizing adverse effects and maximizing therapeutic outcomes. The integration of genomics, proteomics, and other technologies has ushered in a new era of medicine, offering hope for improved treatment efficacy across various diseases, including cancer, cardiovascular disorders, and rare genetic conditions.

2. Genomic Medicine: Decoding the Blueprint of Life

One of the most revolutionary frontiers in medical sciences is the realm of genomics. The decoding of the human genome marked a watershed moment in our understanding of genetic makeup and its implications for health. With the advent of advanced genomic technologies, researchers are now exploring the intricate details of individual genomes, unravelling the mysteries of genetic predispositions to diseases, and paving the way for personalized medicine. CRISPR-Cas9, a powerful gene-editing tool, has opened

new avenues for targeted treatments, raising ethical questions while holding the potential to cure genetic disorders at their root.

CRISPR Gene Editing: Rewriting the Code of Life

The discovery of CRISPR-Cas9 gene-editing technology has revolutionized the field of genetics and opened up unprecedented possibilities for medical interventions. CRISPR enables precise modification of DNA sequences, offering the potential to correct genetic mutations responsible for various diseases. While the ethical implications of gene editing are a subject of ongoing debate, the transformative power of CRISPR cannot be ignored. Researchers are exploring its applications in treating genetic disorders, enhancing agricultural yields, and even addressing infectious diseases by manipulating the genomes of pathogens.

With the developments in gene mapping having caused quite the storm in recent times, physicians, doctors, nanotechnologists and geneticists have become much sought-after. Crops are now being engineered to provide nutrients that help humans to fight diseases. This could lead to a merger of medicine and agriculture. It is also predicted that the emphasis on finding pathways that produce nutraceuticals in plants, especially those with medicinal properties, will increase over the next few years.

Mutation or aberration in genes or parts of genes can lead to diseases. It essentially causes modification of proteins, resulting in changes in physiology of cells. It is this change that causes cancer. It is now possible to find the change in sequence of genes and fashion a new line of medicine.

3. Immunotherapy: Harnessing the Power of the Immune System

Immunotherapy has emerged as a groundbreaking frontier in the treatment of various cancers and autoimmune diseases. By harnessing the body's own immune system to target and eliminate abnormal cells, immunotherapy offers a more targeted and less invasive approach compared to traditional treatments. Checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines are among the innovative immunotherapeutic strategies that are demonstrating remarkable success in clinical trials. The ability to activate the immune system's natural defense mechanisms against cancer marks a departure from conventional treatments like chemotherapy and radiation therapy, offering new hope for patients with advanced-stage cancers. The potential to achieve long-term remission and even cure in certain cancers is a testament to the transformative power of immunotherapy.

4. Artificial Intelligence and Machine Learning in Diagnostics and Treatment

The integration of artificial intelligence (AI) and machine learning (ML) into medical sciences is another frontier that is reshaping the landscape of healthcare. AI algorithms are being employed to analyze vast amounts of medical data, aiding in early diagnosis, treatment planning, and predicting patient outcomes. From image recognition in radiology to predicting disease trajectories based on patient records, AI is enhancing the efficiency and accuracy of medical decision-making. AI is proving invaluable in medical imaging, pathology, and patient management. The development of AI-powered diagnostic tools is enhancing the speed and accuracy of disease detection, while predictive algorithms help identify individuals at risk of developing certain conditions, enabling preventive interventions. The potential of AI in drug discovery and development is also a promising avenue, accelerating the identification of novel therapeutic compounds.

Artificial Intelligence (AI) and Machine Learning (ML) are reshaping the landscape of healthcare, offering unprecedented opportunities to enhance accuracy, efficiency, and personalized care. The significant impact of AI and ML in diagnostics and treatment, and how they are revolutionizing the way we approach healthcare:

- Enhanced Diagnostics

  One of the primary applications of AI and ML in healthcare is in diagnostics. Machine Learning algorithms have proven to be exceptionally adept at analyzing vast amounts of medical data, including images, pathology reports, and patient records. In radiology, for example, AI algorithms can assist in detecting anomalies in medical images, such as tumors or abnormalities, with greater accuracy and speed than traditional methods. This not only expedites the diagnostic process but also reduces the risk of human error.

- Predictive Analytics for Early Detection

  AI and ML algorithms are capable of analyzing patient data to identify patterns and trends that might go unnoticed by human clinicians. This enables predictive analytics, allowing healthcare professionals to foresee potential health issues and intervene early, often before symptoms manifest. This proactive approach to healthcare can significantly improve patient outcomes by enabling timely and targeted interventions.

- Personalized Treatment Plans

  Every patient is unique, and AI and ML technologies facilitate the development of personalized treatment plans. By analyzing genetic data, patient histories, and treatment responses, algorithms can help identify the most effective and tailored interventions for individuals. This move towards precision medicine not only optimizes treatment outcomes but also minimizes adverse effects by considering the patient's specific characteristics and genetic makeup.

- Drug Discovery and Development

  The traditional drug discovery process is lengthy and expensive. AI and ML are streamlining this process by analyzing massive datasets to identify potential drug candidates, predict their efficacy, and optimize formulations. This accelerates the pace of drug development, potentially bringing life-saving treatments to patients faster. Additionally, AI is being utilized to match patients with clinical trials more efficiently, expanding access to experimental treatments.

- Remote Monitoring and Telehealth

  AI-powered devices and applications are transforming the way patients are monitored and managed outside traditional healthcare settings. Wearable devices equipped with AI algorithms can continuously collect and analyze patient data, providing real-time insights into their health status. This enables remote monitoring and timely interventions, reducing the need for frequent hospital visits and improving patient convenience.

5. 3D Printing in Medicine: Building the Future of Healthcare

The application of 3D printing technology in medicine is transforming the way healthcare professionals approach patient care. Customized implants, prosthetics, and even organs can be fabricated with precision, addressing individual patient needs. The ability to create patient-specific models for surgical planning has improved the accuracy and success rates of complex procedures. 3D bioprinting holds promise for the future of organ transplantation, potentially overcoming the shortage of donor organs and reducing transplant rejection rates.

6. Neurotechnology: Unravelling the Mysteries of the Brain

In recent years, the field of neurotechnology has emerged as a groundbreaking frontier, seamlessly blending neuroscience and technology to unravel the mysteries of the human brain. This multidisciplinary approach has opened up new possibilities for understanding, diagnosing, and treating neurological disorders, as well as enhancing human capabilities. From brain-computer interfaces to neuroimaging techniques, neurotechnology is revolutionizing the way we interact with and comprehend the intricacies of the brain.

Neurotechnology encompasses a diverse range of tools and techniques designed to interact with the nervous system. At its core, it leverages advancements in neuroscience, computer science, and engineering to develop innovative solutions for both medical and non-medical applications. Key components of neurotechnology include brain-machine interfaces (BMIs), neuroprosthetics, neurofeedback, and neuroimaging.

Advancements in neurotechnology are providing unprecedented insights into the complexities of the human brain. Brain-machine interfaces (BMIs) are being developed to restore lost sensory and motor functions in individuals with paralysis. Deep brain stimulation (DBS) is proving effective in treating neurological disorders such as Parkinson's disease and epilepsy. Neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), are enhancing our understanding of brain function and paving the way for targeted interventions in conditions like depression and schizophrenia.

BMIs are at the forefront of neurotechnology, enabling direct communication between the brain and external devices. These interfaces hold tremendous potential for individuals with paralysis, as they offer a means to control prosthetic limbs or interact with computers using neural signals. Researchers are also exploring the use of BMIs for cognitive enhancement, paving the way for applications in virtual reality, gaming, and beyond.

Neuroprosthetics are devices that replace or enhance the functionality of impaired neural systems. Cochlear implants for hearing-impaired individuals and retinal implants for vision restoration are examples of neuroprosthetics that have already made a significant impact. As technology continues to advance, neuroprosthetics may evolve to address a broader range of neurological conditions, providing individuals with improved quality of life.

Neurofeedback is a technique that allows individuals to observe and modify their brain activity in real-time. This form of biofeedback is utilized in various therapeutic settings, such as treating attention-deficit/hyperactivity disorder (ADHD) and anxiety. By providing individuals with insights into their brain's functioning, neurofeedback empowers them to learn self-regulation and enhance cognitive performance.

Advancements in neuroimaging techniques have greatly enhanced our ability to visualize and understand the complexities of the brain. Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), and Electroencephalography (EEG) are some of the tools used to study brain structure and activity. These imaging technologies play a crucial role in both research and clinical settings, aiding in the diagnosis and treatment of neurological disorders.

Advancements in neurosciences have paved the way for exploring new frontiers in enhancing cognitive functions and interfacing with the brain. Neuroenhancement techniques, including neuropharmacology and brain stimulation, are being investigated to boost memory, learning, and overall cognitive performance. Moreover, brain-computer interfaces (BCIs) are bridging the gap between the human brain and external devices, offering hope to individuals with paralysis or neurological disorders.

Neurotechnology is reshaping our understanding of the brain and pushing the boundaries of what is possible. From restoring lost functionalities to enhancing cognitive abilities, the applications of neurotechnology are diverse and transformative. As research continues and ethical considerations are addressed, neurotechnology is poised to play an increasingly significant role in shaping the future of healthcare, human-machine interaction, and our overall understanding of the incredible organ that is the human brain. The journey into the realm of neurotechnology is not just a scientific endeavour; it is a quest to unlock the full potential of the human mind.

7. Nanomedicine: Shrinking Treatments, Expanding Possibilities

The convergence of nanotechnology and medicine has given rise to the field of nanomedicine, offering novel solutions to longstanding challenges in healthcare. Nanoparticles, with their unique properties, are being engineered to deliver drugs with precision, target specific cells, and even diagnose diseases at the molecular level. The potential applications of nanomedicine range from targeted cancer therapy to drug delivery across the blood-brain barrier, opening up avenues for more effective and less toxic treatments. As nanomedicine continues to advance, it holds the promise of revolutionizing drug delivery and diagnostics in ways previously deemed impossible.

8. Regenerative Medicine: Healing from Within

Regenerative medicine holds the promise of repairing or replacing damaged tissues and organs, marking a paradigm shift from managing symptoms to achieving functional restoration. Stem cell therapies, tissue engineering, and organ transplantation are key components of regenerative medicine that are pushing the boundaries of what is medically achievable. From repairing heart tissues after a myocardial infarction to regenerating damaged nerves in spinal cord injuries, the potential of regenerative medicine to transform the lives of patients with previously untreatable conditions is immense.

9. Telemedicine: Expanding Access to Healthcare

The rapid evolution of telemedicine has become particularly evident in recent times, with the global response to the COVID-19 pandemic accelerating its adoption. Telemedicine leverages technology to

provide remote healthcare services, enabling consultations, diagnoses, and monitoring from a distance. This approach not only enhances accessibility to medical care but also reduces healthcare disparities, especially in underserved and remote areas. The integration of telemedicine into routine healthcare practices is likely to persist, shaping the future of healthcare delivery.

The new frontiers in medical sciences are reshaping the landscape of healthcare, offering unprecedented opportunities to improve patient outcomes, enhance diagnostics, and revolutionize treatment modalities. From decoding the intricacies of our genetic blueprint to leveraging the power of artificial intelligence, 3D printing, immunotherapy, nanomedicine, neurotechnology, telemedicine and regenerative medicine, the possibilities seem boundless.

However, as we navigate these uncharted waters, ethical considerations, patient safety, and equitable access to these advancements must remain at the forefront of our endeavours. Gene editing demands cautious consideration of unintended consequences and equitable access. Balancing patient empowerment with the privacy of genetic data becomes paramount. These ethical complexities require open dialogue, informed public discourse, and robust regulatory frameworks.

The future of medical sciences is undeniably exciting, and the potential for groundbreaking discoveries and transformative treatments is within reach. The collaborative efforts of researchers, clinicians, and policymakers will play a crucial role in realizing the full potential of these new frontiers and ensuring that the benefits are shared by all. Ensuring equitable access to these advancements is paramount. The digital divide cannot become a health divide, perpetuating disparities in care. Investment in research infrastructure, healthcare education, and community outreach is crucial to bridge the gap between scientific breakthroughs and those who need them most. As we continue to explore and push the boundaries of medical knowledge, the journey into this uncharted territory holds the promise of a healthier and more resilient future for humanity.

So, as we stand gazing at these new frontiers, it's crucial to remember that medical science is not solely a scientific endeavour. It's a tapestry woven with threads of social responsibility and a deep-seated compassion for human suffering too. Embracing this holistic approach, we can navigate these uncharted territories, not just as technological conquistadors, but as responsible stewards of human health and well-being.

This new dawn in medical science holds immense promise, beckoning us to venture beyond the horizon. Armed with scientific ingenuity, ethical responsibility, and a commitment to equitable access, we can embark on a voyage of discovery that not only extends our lifespan, but enriches the very fabric of human existence. The journey may be fraught with challenges, but the destination whispers of a healthier, more resilient future for all. Let us rise to the occasion, step into these uncharted territories, and write the next chapter in the magnificent saga of human health.

(Ravindra Bangar)
Editor

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Research Paper

Assessment of Aspirin Responsiveness by Light Transmittance Aggregometry in Patients with Ischemic Heart Disease – A Study from Southern Rajasthan

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ABSTRACT

The present study was conducted to evaluate the prevalence of aspirin resistance in patients with IHD living in and around Udaipur. Fifty patients of IHD (Group I) either of healed myocardial infarction (>6 months) or angina in whom ischemia can be induced by TMT, and were taking 150 mg of aspirin daily for more than 3 months were selected. Fifty healthy individuals (Group II) were selected as control to know the baseline platelet aggregation in the same age group. Platelet aggregation was assessed employing platelet rich plasma (PRP) on optical aggregometer- ELVI 840.

The study has brought that ten percent of the study population demonstrated aspirin resistance. The incidence of true resistance, that is unresponsive to both, ADP and collagen aggregating agents is 2%, while "Semi responders" constitute 8% of the study population. These patients demonstrated resistance to either of the two aggregating agents. The incidence of clinical resistance in term of recurrence of cardiac event (MI) was observed in 4% of population in whom the true resistance was observed in 2% while 2% were semi responders. Six percent of the study subjects who demonstrated aspirin resistance were semi-responders and all have inducible ischemia and did not develop infarction. Ten percent of the study subjects had recurrent episode of MI in spite of aspirin consumption. In these subjects the true aspirin resistance was observed in 20% of the subjects, twenty percent were semi-responsive, while in 60% aspirin was found to be effective in inhibiting platelet aggregation.

KEYWORDS: Aspirin treatment failure, Aspirin non-responsiveness, PFA-100 device, COX-1inhibition

INTRODUCTION

Cardiovascular diseases account for approximately 12 million deaths annually and are the commonest cause of death globally. Previously considered to be disease of affluent; now it is increasing in developing world too in epidemic proportion. The Asian Indians living in their own country or elsewhere have much higher incidence of coronary artery disease as compared to all other ethnic group. In Indian subcontinent, from 1960's to 1990's the coronary artery disease prevalence increased two folds (from 2% to 4%) in rural and three folds (3.45% to 9.45%) in Urban Indian population[1]. Thus burden of cardiovascular disease in patients and community is enormous.

One way of reducing the burden is to reduce the platelet aggregation in people predisposed to such high risk. Cardiovascular diseases are the result of multiple complex cascade of interaction among the endogenous cells of the arterial wall, the focal haemodynamic environment, blood

components notably monocytes, lipoproteins, inflammatory processes and their mediators and various healing or reparative processes. The role of platelets in thrombosis is central for atherothrombosis.

Platelets are small (2-3 mm in diameter) non nucleated cells containing granules with constituents (e.g. 5-Hydroxytryptamine, catecholamines, and ADP) capable of influencing platelet function. They normally circulate in blood for approximately 10 days before being sequestered in the spleen. Their main function is in primary hemostasis; interacting with injured areas in the vessel wall and form a haemostatic plug that later organizes and incorporates other blood cells and components of the coagulation system[2,3].

Quiescent platelets are discoid in shape and do not adhere to intact endothelium, but a breach of the arterial lining will expose collagen in the deeper tissue layers and this substance activates platelet adhesion, when activated they become irregular and, form pseudopodia. The exposure of sub-endothelial collagen and the release of von Willebrand factor results in binding of these substances to glycoproteins IA/ IIA and IB of the platelet surface[4,5].

For platelets to interact with the endothelium, the platelet glycoproteins IIB-IIIA must first undergo a conformational change. In addition to shape change and adhesion, activated platelets release from their "dense bodies" various agonists, including serotonin and ADP, which intensify aggregation, as does thromboxane A_2 (TXA_2), besides being vasoconstrictive. TXA_2 is derived from arachidonic acid, a substance present in the phospholipids of the platelet membrane. The other inclusion system of platelets, the "alpha granules", contain P-TG (β-thromboglobulin), PF-4 (Platelet factor four), PDGF (Platelet Derived Growth Factor) and t PAI-2 (tissue plasminogen Activator inhibitor); these are also released when thrombocytes are activated and further intensify platelet aggregation.

In opposition to these aggregation promoting factors, the vascular endothelial cells synthesize prostacyclin (PGI_2) which, by stimulating CAMP, inhibit platelet aggregation and release. If endothelial cells are injured, several factors are released e.g. 11 platelet activating factor (PAF), a potent stimulus for platelet aggregation. The endothelial cells also synthesize and release "endothelium derived relaxing factors" (EDRF), one of these is nitric oxide (NO), which like $PG_{1\alpha}$ inhibits platelet aggregation and stimulates vasodilation[5]. The action is mediated by an increase of platelet cAMP and cGMP.

Platelets have been implicated as being pathophysiologically important in hypertension and ischemic heart diseases. They might contribute to coronary artery disease in at least two ways; one by thrombus formation caused by platelet activation in the presence of vascular damage and secondly as a source of mitogenic influence (platelet derived growth factor)[6,7].

In the treatment of CAD aspirin has remained cornerstone of therapy in both primary and secondary prevention of death due to CAD owing to its antiplatelet functions[8, 9]. Aspirin is being used for last 2 centuries. "Willow bark" contains salicin from which salicylic acid is derived. It was used for fever in 18th century as cheap substitute for imported cinchona bark. Its antiplatelet action has recently been recognized[10]. Today nearly all patients of CAD and peripheral vascular disease are receiving this drug.

Aspirin is a cyclo-oxygenase inhibitor thus irreversibly blocks the formation of thromboxane A_2, a potent mediator of platelet aggregation which converts arachidonic acid to prostaglandin G_2. Platelets does not contain nucleus, so once inhibited it can't form cyclo-oxygenase. The enzyme inhibition is permanent and irreversible. Other effects of cyclo-oxygenase inhibition are the block of production of prostacyclin. $PG_{1\alpha}$ that opposes platelet activation. Aspirin inhibits the release of ADP, cationic proteins, PGE_2. $PGE_{2\alpha}$ and phospholipase from the granules of platelets. The use of aspirin as anti thrombotic drug therapy started in 1983 with publication of the Veterans administration cooperative study. This study decreased 1 year event rate by 5% as compared with placebo (10.1%)[11].

A larger number of trials including antiplatelet trialists' collaboration meta analysis, the largest trial ever conducted on aspirin efficacy has proved that aspirin in effective in reducing deaths from myocardial infarction from 25%-68%[12]. However, the antiplatelet effect of aspirin has not been observed to be uniform on all human population and relative risk of recurrent vascular events in patients receiving aspirin therapy remains high (8-18% after 2 years)[13]. Aspirin resistance has been reported to occur in 5% to 45% of general population and its detection is of clinical importance.

The initial evidence that some patients may be resistant to aspirin came from study by Mehta and associates who reported that 30% of patients had minimal inhibition of platelet aggregation after single 150 mg of dose of aspirin[14]. The significant studies by Grundmann and co-workers in ischemic stroke patients with high dose of aspirin proved aspirin resistance to be 34%[15]. Gum and associates conducted studies on 326 patients of IHD and reported a 5% incidence of aspirin resistance by optical platelet aggregation[16]. In a subgroup study of the Heart Outcomes Prevention Evaluation (HOPE) trial sample, Eikelboom and colleagues observed increased adverse events in individuals exhibiting aspirin resistance during a 5-year follow-up. As a measure of *in vivo* thromboxane production, the urinary concentration of 11-dehydrothromboxane B2 was determined. For every quartile that 11-dehydrothromboxane B2 levels increased, the adjusted chances for the composite end-point of myocardial infarction (MI), stroke, or vascular death also increased[17].

Despite consistency of such observation, the prevalence of aspirin resistance has been variable in different populations and there is lack of standardized diagnostic criteria on a single validated method of identifying affected individuals to have aspirin resistance. It has led to wide range of population estimates[18]. Prospective studies have demonstrated that the decrease responsiveness to aspirin therapy is associated with an increased risk of clinical events[19,20].

Aspirin resistance has been observed to affect patients of various categories and healthy controls without vascular disease as well[15,21,22]. Provided more than 12 million deaths caused by CAD annually, even a 5-10% prevalence of aspirin resistance affects more than a million patients[16]. Therefore, it is pertinent to take into account the aspirin resistance while

treating patients with ischemic cardiovascular diseases.

The present study, therefore, has been envisaged to study aspirin responsiveness in patients with ischemic heart disease consuming aspirin 150 mg and living in and around Udaipur.

MATERIAL AND METHOD

The study was conducted on male patients of IHD who were stable in their symptoms, attending OPD or admitted in the wards of Maharana Bhupal Hospital attached to R.N.T. Medical College, Udaipur. After informed consent a total number of 50 subjects were selected for the study in each group:

The study groups included in study are as follows:

Group I : 50 patients of ischemic heart disease (IHD) who are stable in their symptoms and taking 150 mg of aspirin daily from last 3 or more months.

Group II: 50 healthy individuals without any evidence of ischemic heart disease.

Patients with ischemic heart disease (IHD) were selected based on the following investigational criteria:

1. ECG:
   (a) Documentation of old healed myocardial infarction.
   (b) ST depression of ⩾2mm in consecutive leads with or without symptoms.
2. ECHO: Regional wall motion abnormalities (RWMA)
3. Positive TMT:
   (a) Horizontal or down sloping ST segment depression of >1 mm from previous level during TMT with or without symptoms.
   (b) Junctional depression with slowly rising ST slope that remains depressed 1.5 mm or more than 0.80 m seconds after the J point.
   (c) Slowly up sloping ST segment depression with the ST segment being depressed in excess of 2.5 mm, 80 m seconds after the J point.
   (d) Down sloping or flat, ST segment depression in excess of 2.5 mm.
   (e) Horizontal or Down sloping ST segment depression appearing during the first stage of exercise and/or persisting beyond 8 minutes in the recovery phase.
   (f) Complex ventricular, ectopic activity, including multiform ventricular ectopic beats, or runs of ventricular tachycardia or occurrence of ventricular fibrillation.

Exclusion Criteria:

The following subjects were excluded from the study-

1. Those were taking ticlopidine, dipyridamole, clopidogrel, heparin, LMWH (low molecular weight heparins) and corticosteroids and other non steroidal anti-inflammatory drugs.
2. Haemoglobin 8 gm/dL
3. History of myelo - proliferative syndrome & malignant paraproteinemias.
4. Family or personal history of bleeding disorders.
5. Patients with diabetes, hypertension.
6. Patients with peripheral vascular diseases.

Method:

Venous blood samples (9 ml) was collected in the morning in a fasting state without undue pressure of stable cardiac patients of age more than 40 yrs after brief history, physical examination and written consent. Specimens were kept at room temperature and subjected within 1 hour for estimation of platelet aggregation on ELVI-840 aggregometer and Omniscribe chart recorder.

PLATELET AGGREGATION[23]

Most important function of platelets is their role in haemostasis i.e. adhesion to the damaged tissue surfaces and cohesion to one another. This cohesion phenomenon is known as aggregation and may be initiated by a variety of substances including collagen, adenosine 5-diphosphate (ADP), epinephrine, arachidonic acid, serotonin and ristocetin. Aggregation is one of the numerous in vitro tests performed as a measure of platelet function. The described procedure is turbidimetric method of measuring the effect of collagen, ADP and epinephrine on platelets, better termed as light transmittance aggregometry (LTA).

Reagents:

1. 3.8 per cent citric acid (Trisodium salt dehydrate): Prepared by dissolving 3.8 gm citric acid in 100 ml of deionized water.
2. Tris buffer: Tris (hydroxy methyl), methylamine, 1.21 gm. (0.01M), disodium ethylene diamine tetra acetic acid 0.372 gm (0.001 M), sodium chloride 8.76 gm. (0.15 M), dissolved in distilled water adjusted to pH 7.5 with hydrochloric acid and made up to one litre with distilled water.
3. ADP reagent: Adensoine 5-diphosphate lyophilized with buffer salts (supplied by sigma diagnostics). ADP solution was prepared by reconstituting ADP reagent with 1.0 ml deionized water to yield solution containing ADP 2x1 04mol/lit. It was swirled to mix and allowed to stand at room temperature (18-26°) for 15 minutes before use. It should be kept at room temperature only for duration of testing. The reconstituted reagent is stable for one month if stored in refrigerator (2° to 6°C).
4. Collagen Reagent: Collagen (calf skin) acid soluble, approximately 2 mg lyophilized with buffer salts, Collagen solution was prepared by reconstituting a vial of collagen reagent with 1.0 ml deionized water. The, vial was allowed to stand undisturbed for at least 15 minutes at room temperature before use. Warming to 37°C may be necessary for complete dissolution. It was swirled to mix prior to each assay. It should not be vertexed. The solution should be kept at room temperature only for the duration of testing. It is usually stable for at least 2 weeks refrigerated (2° to 6° C). Stability may be extended by freezing.

INSTRUMENTS AND MATERIALS REQUIRED

(1) Instruments:

1. Platelet aggregometer (ELVI 840).
2. Chart recorder (Omniscribe recorder dual pen type L176 2USA)

(2) Materials:

1. Cuvette 250 µl
2. Teflon coated magnetic stirring bars (micro agitators)
3. Pipettes with disposable plastic tips 50 µl and 250 µl.
4. Centrifuge machine.
5. Plastic tubes with caps.
6. Plastic transfer pipettes.

A. Specimen collection:

Blood was collected by avoiding stasis and contamination with tissue fluids into plastic tubes containing 0.1 ml buffer and 3.8 per cent sodium citrate in a ratio of blood to anticoagulant in a ratio of 9: 1.

B. Preparation of platelet rich plasma (PRP):

(i) The anticoagulant sample was centrifuged at 400 rpm, for 10 minutes.

(ii) PRP was removed carefully using a plastic transfer pipette.

(iii) PRP was expelled into a plastic tube and covered and kept at room temperature for duration of the test.

C. Preparation of platelet poor plasma (PPP):

(i) It was prepared by re-centrifuging the PRP at 6000 rpm for 10 minutes.

(ii)Supernatant was transferred to a labelled PPP tube, covered and kept at room temperature for the duration of test.

The platelet count of PRP was adjusted to the range of 4 to 5 lac/cu mm when necessary by addition of autologous PPP to PRP sample. The caution should be taken to assay platelet aggregation within 30 minutes of collection of test samples.

Aggregating agents - ADP and Collagen

ADP - ADP induced aggregation may occur in one or two phases and it may be followed by rapid disaggregation which may be seen in normal man without any hemorrhagic disease.

Collagen - Collagen induced platelet aggregation may occur in an - irreversible single phase curve or a reversible single phase curve depending on the collagen concentration in the PRP.

Procedure:

After preparing PRP and PPP the aggregation was recorded as follows:

1. Cuvette with PRP was introduced into the aggregometer.
2. The electromagnetic agitation was started by means of stiffed control after having introduced a small stiffing bar into the sample.
3. Agitation speed was maintained at 1000 rpm.
4. Baseline of the recorder was adjusted by means of the zero control.
5. The cuvette with PRP was removed and cuvette with PPP was inserted.
6. By means of gain control the maximum excursion of the pen on the recorder was adjusted.
7. Cuvette with PPP was removed and the cuvette with PRP was reinserted and it was readjusted if necessary by means of the zero control.
8. The sliding of the recorder paper was started.
9. The aggregating agents (ADP and Collagen) were added to the PRP by means of micropipette (50 µl).

The aggregation was recorded for a minimum of five minutes and results were expressed as percentage aggregation.

$$\text{Percentage Aggregation} = \frac{90 - CR}{90-10} \times 100$$

$$= \frac{90 - CR}{80} \times 100$$

CR is chart reading in terms of number of segments.

Aspirin resistance - Platelet aggregation induced by ADP and Collagen in patient receiving 150 mg of aspirin, more than 60% will be taken as aspirin resistance.

Table 1 shows the profile of 50 male patients of ischemic heart disease, selected for the study. There were 32 patients who had sustained myocardial infarction in the past and were stable in their symptoms. Their mean age was 62.53 years and they were regularly taking 150mg of aspirin daily from last 2 years or more. Eighteen patients were of ischemic heart disease, proved on TMT. Their mean age was 57.7 years and mean duration of aspirin consumption was 4 years and 4 months.

Table 1: Profile of Study Subjects (IHD)

	No. of Patients	Mean age (years)	Mean duration of Aspirin treatment
Old MI	32	62.53	2 years 10 months
IHD – TMT positive	18	57.72	4 years 4 months

MI – Myocardial Infarction, IHD – Ischemic Heart Disease, TMT – Tread Mill Test

Table 2: Platelet Aggregation in Healthy Individuals

	Platelet Aggregation (Percent)	
	ADP	**COLL**
Mean	57.00	52.87
SD ±	9.36	9.88
SE ±	1.32	1.40

Platelet aggregation profile of 50 healthy individuals (Group II), induced by ADP and Collagen have demonstrated that their mean ADP induced platelet aggregation was 57± 9.36 percent, while collagen induced platelet aggregation was 52.87±9.88 percent (Table 2).

Table 3: Platelet Aggregation in Patient with IHD taking Aspirin (150mg)

	Age	**Platelet Aggregation (Percent)**		**Duration of Aspirin Consumption (Months)**
		ADP	**COLL**	
Mean	60.80	32.23	27.43	40.22
SD ±	8.24	16.22	18.88	40.30
SE ±	1.17	2.29	2.67	5.70

Table 3 depicts the platelet aggregation of 50 patients of ischemic heart disease who were taking aspirin (150 mg) daily for more than 3 months. The age varies from 44 to 78 years. The mean duration of aspirin consumption was 40.22±40.30 months. The mean platelet aggregation was 32.23±16.22 percent and 27.43±18.88 percent induced by ADP and Collagen respectively. There are three patients each in ADP and Collagen subsets who demonstrate aggregation of more than 60 percent.

Table 4: Inhibition of Platelet Aggregation by Aspirin (150mg) in Patient with IHD

	Age	**Platelet Aggregation (Percent)**		**Duration of Aspirin Consumption (Months)**
		ADP	**COLL**	
Mean	60.80	66.78	72.58	40.22
SD ±	8.24	17.64	18.88	40.30
SE ±	1.17	2.49	2.67	5.70

The percentage inhibition of platelet aggregation by 150 mg of Aspirin in patients with Ischemic Heart Disease has been shown in table 4. On further analysis of the results, it was observed that except 3 patients (cases 2, 10 & 44) all have demonstrated more than 60 percent inhibition of platelet aggregation induced by ADP. Likewise, 3 patients (cases 18, 26 & 44) also demonstrated platelet aggregation less than 40 percent with Collagen.

Table 5: Profile of Patients Demonstrating Aspirin Resistance

S. No.	ADP ($2x10^{-4}$mol/L)			
	Age	**Diagnosis**	**Duration of Aspirin Treatment**	**Platelet Aggregation (Percent)**
1	55	TMT moderately positive	8 months	65.00
2	68	TMT strongly positive	10 years	68.75
3	58	Recurrent MI 1. Inferior Wall MI 2. Anterior Wall MI	8 years 6 months	75.00

TMT – Tread Mill Test MI – Myocardial Infarction

The profile of three patients who demonstrated aspirin resistance induced by ADP has been given in table 5.Their age was ranging from 55 to 68 years. Two patients were of IHD proved on exercise Test, while one patient was of recurrent myocardial infarction who sustained inferior and anterior myocardial infarction in spite of regular aspirin consumption for last 8 and half year. The aspirin, in this patient, was able to inhibit platelet aggregation only to the extent of 25 percent.

Table 6: Profile of Patients Demonstrating Aspirin Resistance

S. No.	Collagen (0.2µg/ml)			
	Age	**Diagnosis**	**Duration of Aspirin Treatment**	**Platelet Aggregation (Percent)**
1	64	Recurrent MI 1. Anterior Wall MI 2. Inferior MI	12 years	68.75
2	60	TMT Positive	5 years	62.50
3	58	Recurrent MI 1. Inferior Wall MI 2. Anterior Wall MI	8 years 6 months	68.75

TMT – Tread Mill Test MI – Myocardial Infarction

On analysis of profile of patients who manifested aspirin resistance based on Collagen aggregant, it was found that one patient of recurrent myocardial infarction is common in table 5 and 6. Who demonstrates true resistance i.e. both ADP and Collagen induced aggregation more than 60 percent and sustained second myocardial infarction. In remaining two patients one was of recurrent myocardial infarction and other was of inducible myocardial ischemia. In both the patients of recurrent infarction, the duration of aspirin administration was more than 8 years and both were demonstrating platelet aggregation more than 68 percent (Table 6).

Table-7: Profile of Patients with Recurrent Myocardial Infarction

Case No.	Age	Name	Duration of Aspirin Treatment (months)
5	60	Nathulal	60
16	66	Mohan Singh	30
18	64	Kachrulal	144
24	72	Lalu Ram	50
44	58	Dalpat	102

The profile of patients who had recurrent myocardial infarction inspite of aspirin therapy showed that out of 5 patients, one (case number 44) showed true aspirin resistance in whom both ADP and collagen caused more than 60% platelet aggregation. Case number 18, on the other hand, was aspirin semi-responder. Where ADP induced platelet aggregation was 33.75% but collagen induced platelet aggregation was 68.75%. Rest of three cases were aspirin responsive (Table 7).

DISCUSSION

The present study was conducted to observe the prevalence of aspirin resistance among patients of Ischemic Heart Disease (IHD) who are residing in and around Udaipur and taking 150 mg of aspirin for more than 3 months regularly.

Fifty male patients of ischemic heart disease were selected for the study and 50 healthy volunteers were also taken as control for establishment of normal platelet aggregation. All the study subjects were kept overnight fasting and venous blood samples were collected in the morning for platelet aggregation. All the blood samples were subjected for estimation of platelet aggregation using ELVI 840 aggregometer and Omniscribble chart recorder (LTA).

Platelet aggregation measurement in healthy individuals (Table 2) shows that mean aggregation induced by ADP and collagen are 57.00±9.36 and 52.87±9.88 percent respectively. Based on these limits 60% was taken as cut off point. Platelet aggregation more than 60% was taken as aspirin resistance. If both ADP and Collagen induced platelet aggregation is more than 60% than patients were labelled to have "true resistance", while, if one aggregant showed aggregation more than 60% and other less than that they were labelled as "semi responders".

Profile of 50 patient of IHD selected for the study showed that 32 patients were of healed MI and 18 patients were of Angina. All the patients were stable in their symptoms and were taking Aspirin 150 mg daily for than 2 years and 4 years respectively (Table 1).

The mean platelet aggregation induced by ADP and collagen were 32.23±16.22 and 27.43±18.80 percent which reflected good aspirin response. However, on careful analysis of observations (Table 3) 3 patients[2,10,44] showed aspirin resistance (aggregation > 60%) in ADP Induced aggregation and 3 patients[18,26,44] in collagen induced aggregation. In all these patients the percentage of inhibition of platelet aggregation by 150 mg of Aspirin was less than 40% (Table 4).

On further analysis of patients demonstrating aspirin resistance (Table 5, 6); one patient who demonstrated ineffectiveness of aspirin in inhibiting platelet aggregation by both the aggregants had true resistance. He also had recurrent MI in spite of aspirin consumption for last 8.5 years. The other 4 patients were semi-responders who demonstrated failure of aspirin activity with either of aggregants.

The present study therefore brings the fact that aspirin resistance in this area is around 10% out of which 2% is the true resistance and 8% showed semi-responsiveness. Moreover aspirin resistance and duration of aspirin consumption have proportionate relation as the majority of patients demonstrating aspirin resistance were consuming aspirin for more than five years (Figures 1and 2).

The overall prevalence of aspirin resistance in different studies varies from 8% to 45%[12,24,25]. However the dose of aspirin resistance varies in different studies from 75 mg to 325 mg /day as well as methodology used to define aspirin resistance.

Aspirin is the cornerstone of antiplatelet therapy in cardiovascular medicine. Its role in the secondary prevention of vascular events has been proven beyond any doubt. A recently published meta-analysis of 287 randomized trials of antiplatelet therapy by the Antithrombotic Trialists Collaboration has shown a significant reduction in the combined end-point of any serious vascular event in a cohort of high-risk patients with atherothrombotic diseases[26]. However, a substantial proportion of patients manifest "breakthrough" events despite regular intake of aspirin. It is estimated that one in eight high-risk patients suffers from the recurrence of a vascular event within the next 2 years despite regular daily aspirin therapy[27]. Also, by using different methods of measuring platelet activity, several studies have demonstrated marked individual variations in the response to treatment with aspirin[16,24,28,29]. Based on the clinical and laboratory evidence of reduced or absent response to treatment with aspirin in some patients, the concept of "aspirin resistance" has emerged, and has caught the attention of both professionals and the mass media[30].

Unfortunately, aspirin resistance remains a poorly defined term. There are conflicting reports on the incidence and clinical relevance of this phenomenon as this term is being used to describe a number of different phenomena. These include the inability of aspirin to either protect individuals from thrombotic complications; or failure to cause prolongation of bleeding time, or inhibit platelet aggregation ex vivo. or inhibit platelet thromboxane formation[31,32].

Perhaps a clinical definition of aspirin resistance as the failure of the drug to prevent an ischemic event despite regular intake of appropriate doses is the most relevant for practising physicians[31]. It is well known that platelet inhibition is not a uniform process, and considerable inter- and intra-individual variations exist in the antiplatelet effect of aspirin. This mandates functional and biochemical in vitro tests to individualize treatment, and possibly identify the subgroup of patients at risk for future vascular events.

Traditionally, platelet function has been assessed by measuring platelet aggregation in platelet-rich plasma using an optical aggregometer. This test is widely available, and has been used in many investigational studies. Based on this method, 5% and 24% of patients with stable cardiovascular disease on aspirin therapy (325mg/day for at least a week) were defined as "resistant" and "semi responders", respectively[31].

Recently, simpler and more rapid tests of platelet function have been developed. Whole-blood aggregometry is more user

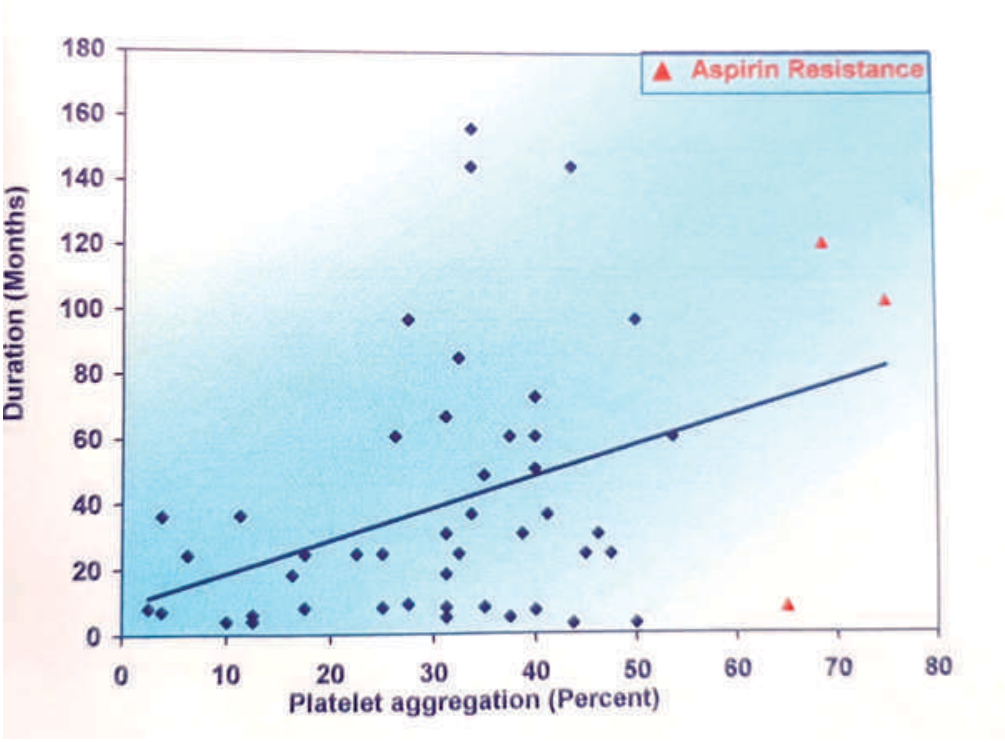

Figure 1: Correlation of platelet aggregation induced by ADP with duration of aspirin therapy

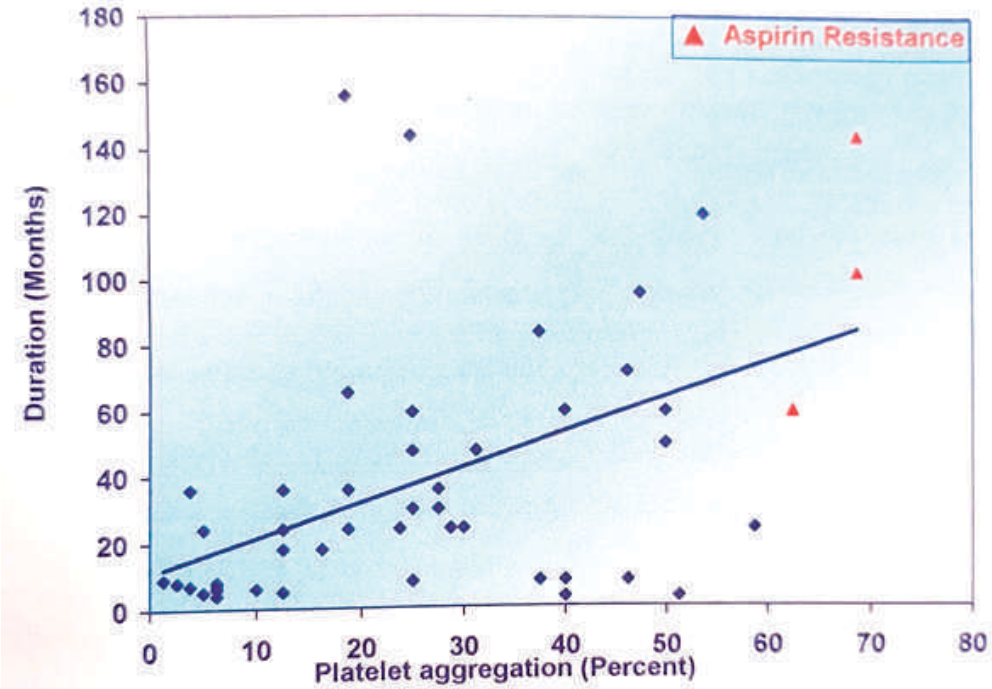

Figure 2: Correlation of platelet aggregation induced by collagen with duration of aspirin therapy

friendly as it eliminates the step of preparing platelet rich plasma. However, the results of this test have not correlated well with those from optical aggregometry[32]. In clinical practice, PFA100 (Dade Behring, Deerfield, Illinois) is the most appealing test at present for the assessment of platelet function. It is a semi-automated analyzer developed to allow the rapid assessment of platelet function using whole blood. The results are easily reproducible and correlate well with the results of optical aggregometry[32,33].

A nonspecific measure of platelet function is the assessment of bleeding time[2, 27]. Other less extensively studied tests include the platelet aggregate ratio, the platelet reactivity index, and the rapid platelet function assay (RPFA)[32,34]. Recently, urinary 11-dehydrothromboxane B_2 levels (a stable metabolite of thromboxane A_2 [TxA_2]) has been used as a marker of suppression of thromboxane formation with aspirin therapy[19]. Since the levels reflect both platelet and non-platelet sources of thromboxane generation, this test lacks specificity. Collectively, these techniques identify an inadequate response to aspirin in 5-60 percent of patients with different vascular atherothrombotic diseases. It is difficult to assess which of these techniques is the most accurate and specific measure of aspirin resistance unless the results are supported by direct comparison with the clinical outcome.

Weber and co-workers classified aspirin resistance into 3 distinct types using simple biochemical tests, and functional *in vitro* studies[31].

TYPE I RESISTANCE (PHARMACOKINETIC TYPE):

When aspirin was taken orally for five days at a dose of 100 mg/day, aspirin responders showed greater than 95% inhibition of thromboxane production and of collagen-induced platelet aggregation as evaluated in vitro. Oral aspirin use for five days did not reduce either thromboxane production or collagen-induced platelet aggregation in patients with "type I resistance" (pharmacokinetic type). However, the addition of 100 μm of aspirin *in vitro* to the platelet-rich plasma significantly changed both of these characteristics. This implies that the pharmacokinetics of low-dose aspirin may vary significantly.

TYPE II RESISTANCE (PHARMACODYNAMIC TYPE):

Neither the oral aspirin consumption nor the in vitro addition of 100 μm of aspirin affected any of the platelet activities. Although the exact mechanism of this kind of resistance is unknown, it may be connected to the enzymatic pathways genetic variation and aspirin sensitivity.

TYPE III RESISTANCE (PSEUDO-RESISTANCE):

Neither the oral aspirin consumption nor the in vitro addition of 100μm of aspirin affected any of the platelet activities. Although the exact mechanism of this kind of resistance is unknown, it may be connected to the enzymatic pathways, genetic variation and aspirin sensitivity. It is possible that certain aspirin-resistant individuals have higher platelet sensitivity to collagen[35]. It's unclear whether this variation has any clinical significance. It is unknown if this change, as assessed in artificial *in vitro* settings, will correspond to a reduced aspirin`s antithrombotic action *in vivo.* 101 It has been suggested that raising the aspirin dosage may help people with type I resistance. Furthermore, additional antiplatelet medications may be beneficial for people with types II and III resistance. The classification and clinical importance has not been investigated yet, though. This problem can only be adequately addressed by prospective follow-up studies in aspirin-resistant patients and their clinical connection.

A few long-term follow-up clinical studies have suggested that aspirin resistance is indeed clinically important[25,36-38].

Grotemeyer and co-workers in a cohort of 180 patients with stroke found that nearly 30% of patients were aspirin non-responders. At a follow-up of 2 years, major clinical vascular end-points were significantly higher in this group as compared to aspirin responders (40% v/s 4.4%, $p<0.0001$). The methodology used by them was platelet reactivity; aggregation induced by blood collection[28].

Mueller and co-workers, in 100 patients undergoing peripheral balloon angioplasty reported an 87% higher risk of re-occlusion on follow-up in patients who failed to show an appropriate response to aspirin[36].

Grundmann and co-workers found that an aspirin non responder status was seen in 34% of patients with recurrent cerebrovascular ischemic events, despite regular use of aspirin for more than 60 months[15].

Buchanen and Pappas, independently conducted aspirin resistance studies on various study groups and healthy controls without vascular diseases, have also shown to have resistance by laboratory testing[21,22].

Chen and associates reported 19.2% incidence of aspirin resistance as defined by Ultra RDFA among 151 patients with coronary disease[20], using ultra rapid platelet function analyser defined aspirin resistance as ARU(ASPIRIN RESPONSE UNITS) >550.

Gum and co-workers reported 5% incidence of aspirin resistant and 23.8% were aspirin semi responders. By PFA-100 (platelet function analysis), 9.5% were aspirin resistant. They found no difference in aspirin sensitivity by race, diabetes, platelet count or liver diseases[19]. They used both optical platelet aggregation using ADP and arachidonic acid as aggregants and PFA (platelet function analyser) for determination of aspirin resistance.

Macchi and co-workers studied 160 stable cardiac patients using PFA-100 (platelet function analyser) and found aspirin resistance in these patients to be 29.2%[39]. Epinephrine closure time less than 186 sec was taken as aspirin resistance by them.

Sibi and co-workers using optical platelet aggregation studied 150 mg dose of aspirin in 75 stable cardiac patients and

reported aspirin resistance to be 26% in studied patients[40]. Methodology used by them was optical platelet aggregation using arachidonic acid and ADP.

Anderson and co-worker studied 129 stable CAD patient using PFA-100 with aspirin resistance define as epinephrine closure time < 196 seconds and reported aspirin resistance of 1.35%[29].

Serum markers such as soluble CD40 ligand and P selection have also been used as markers of platelet activation with variable results[37].

Two recently published studies have highlighted adverse outcomes with aspirin resistance in a larger cohort of patients, and after a longer follow-up period.

In a subgroup analysis from the Heart Outcomes Prevention Evaluation (HOPE) trial population, Eikelboom and Co-workers (2002) found that individuals with aspirin resistance had more bad outcomes during a 5-year follow-up. As a measure of *in vivo* thromboxane production, the urinary concentration of 11-dehydrothromboxane B_2 was determined. With each rising quartile of 11-dehydrothromboxane B_2 levels, the adjusted chances for the composite end-point of myocardial infarction (MI), stroke, or vascular death rose. Individuals with insufficient suppression of TXA_2 and consequent aspirin resistance in the highest quartile were 1.8 times more likely to have composite end-points than patients in the lowest quartile. Likewise, there was a 3.5 times greater risk of cardiovascular mortality and a 2- times higher risk of MI in each group. This substantial and graded correlation between aspirin resistance in the laboratory and unfavourable outcomes was not correlated with traditional risk factors for atherothrombotic vascular diseases[41].

During a mean follow-up period of 679±185 days, Gum and Co workers (2003)[19] emphasised the natural course of aspirin resistance in stable patients with cardiovascular disease. Aspirin resistance was linked to a significantly higher risk of composite end-points such as death, MI, or cerebrovascular accident (CVA) in this prospective, blinded study involving 326 patients when compared to aspirin-responsive patients (24 percent v/s 10 percent, respectively; p=0.03, hazard ratio 3.12)[19].

It is interesting to note that among 50 patients of IHD 32 patients were of healed MI and 5 patients demonstrated recurrent MI in spite of aspirin therapy (Table 7). In these patients of recurrent MI, one patient demonstrated true aspirin resistance, clinically as well as on laboratory study. Aspirin in this patient could not inhibit Platelet aggregation induced by ADP and Collagen. The other patient (case no 18) was aspirin semi-responder while remaining three patients were aspirin responsive. It is clear from the above data that among the patients of IHD who demonstrated recurrence of MI in spite of aspirin therapy aspirin resistance should be seriously thought of Because, as it is evident in the present study. 20% of these patients may have true aspirin resistance and need alternative or combined therapy with other antiplatelet drugs.

Aspirin blocks the formation of TxA_2, a potent vasoconstrictor and platelet agonist by irreversibly inhibiting the enzyme platelet cyclo-oxygenase (COX) (Fig.3). COX has two isoforms of clinical relevance COX-1 isoenzyme is expressed in mature human platelets. The therapeutic efficacy of aspirin in atherothrombotic vascular disease has been clearly attributed to its inhibition of COX-1 activity[38,42]. Importantly, in the low doses necessary to achieve platelet inhibition, aspirin does not inhibit endothelial cell prostaglandin synthesis, particularly prostacyclin, which is a potent vasodilator[33,34]. COX-2 isoenzyme plays a dominant role in the processes of inflammation andcancers[38]. Aspirin acts as an anti-inflammatory agent due to the inhibition of COX-2 activity at higher doses. Although much is currently known about effect of aspirin on platelets, the mechanism by which some patients are resistant to this effect has not been clearly established.

A number of extrinsic variables can alter aspirin`s capacity to deactivate platelets. Aspirin`s antiplatelet impact has been demonstrated to be influenced by smoking elevated cholesterol levels, and circumstances linked to an accelerated platelet turnover[43,44]. While full inhibition of COX-1 is anticipated with low-dose aspirin, greater doses may be needed for certain people to have the desired antiplatelet effect.

Helgason and co-workers in patients with stroke reported the effect of dose escalation of aspirin in non-responders as judged by aggregation studies. An initial 25% incidence of aspirin resistance (daily dose 325 mg) fell to 8% with dose escalation up to 1300 mg. However, a recently published meta-analysis does not support this contention, and it may not be practical in many patients due to gastrointestinal side-effects[24].

Secondary aspirin resistance may be influenced by certain medication interactions, particularly those involving non-steroidal anti-inflammatory medicines (NSAIDs). Since aspirin and NSAIDs are both frequently given medications, it is possible that many people are taking both on a long-term basis. Given that both of these medications function by suppressing the COX enzyme, there is a chance that they will interact competitively. NSAIDs, on the other hand, are reversible inhibitors of this enzyme, unlike aspirin. Aspirin`s long-lasting antiplatelet activity has been demonstrated to be blocked by NSAIDs (such as ibuprofen), which modifies the drug`s cardioprotective effects. In individuals who initially react to aspirin, this can potentially result in secondary aspirin resistance[43]. This is because an NSAID competitively inhibits the active site inside the COX-1 channel, preventing aspirin from reaching its target[44]. Furthermore, there is currently proof that this medication combination has negative long-term clinical outcomes[21,45].

MacDonald and Wein[46] reported a cohort of patients' secondary prophylaxis with aspirin, and highlighted that on concomitant administration of ibuprofen was associated with a significant increase in the all cause mortality as well as cardiovascular mortality on long-term follow-up. The absence of COX-2 in mature human platelets explains why selective COX-2 inhibitors (coxibs) do not inhibit the effects of low-dose aspirin on platelet function in comparison with ibuprofen[44,47]. These drugs would logically seem preferable to ibuprofen when

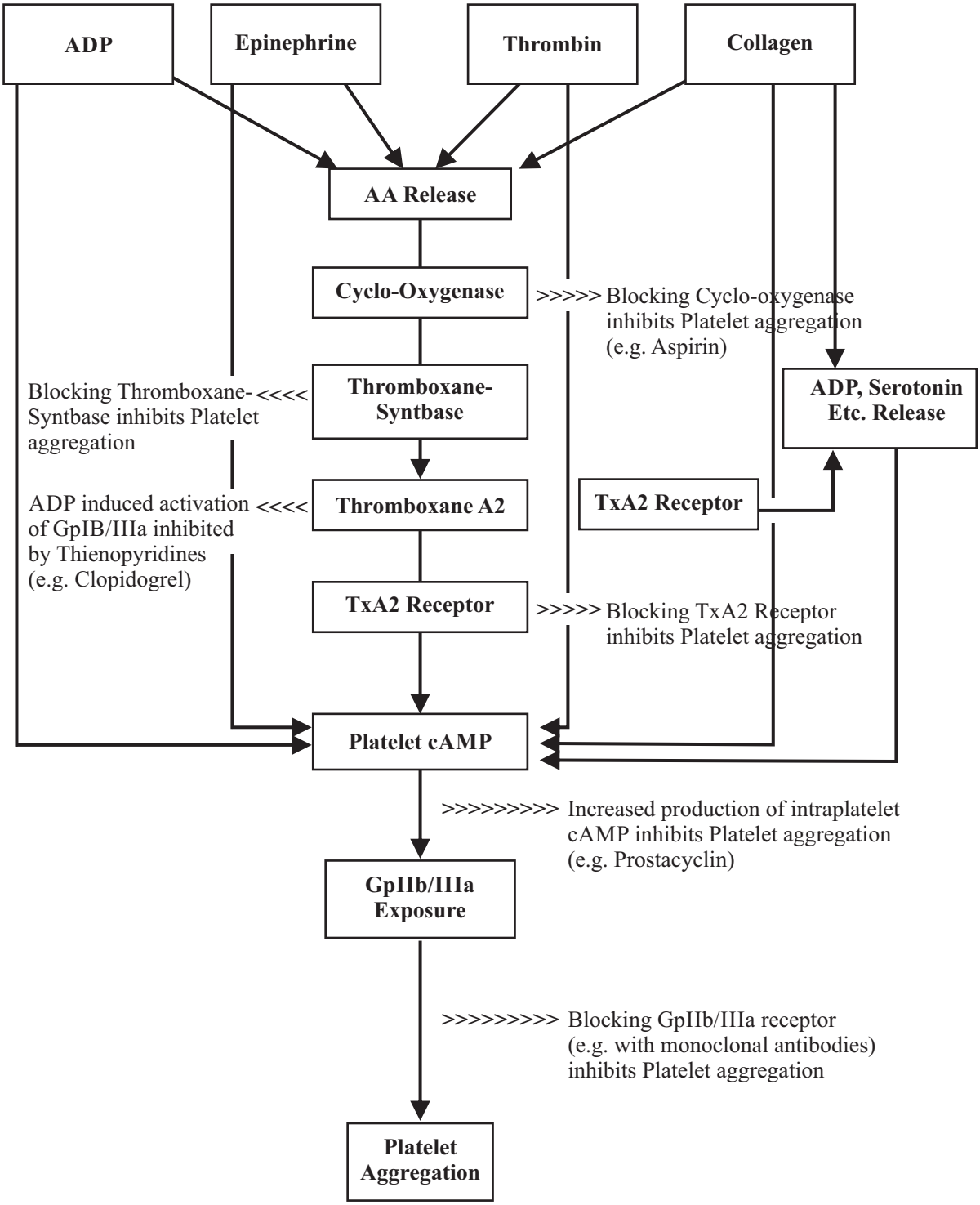

Figure 3: Platelet activation mechanism leading to platelet aggregation

patients taking aspirin for cardio protectiveness require chronic treatment with NSAIDs.

A number of intrinsic mechanisms have been postulated to cause aspirin resistance. The inability of treatment to sufficiently reduce TXA_2 Synthesis is a critical factor in the pathophysiology of aspirin resistance [19, 48]. The emergence of aspirin resistance has been linked to COX-2, despite aspirin`s almost 170-fold greater potency in inhibiting COX-1. It has long been assumed that mature platelets are only COX-1 isoenzyme-containing. 99 Contemporary data, however still subject to debate, has demonstrated that COX-2 mRNA is present in platelets[48,49]. Patients differ in the extent of their COX-2 expression, and some may express COX-2 at higher levels than others, particularly under stress. Due to low dosage Aspirin`s inability to block the COX-2 enzyme, individuals on aspirin treatment may have an alternative pathway for platelet-mediated thromboxane synthesis, which might lead to aspirin resistance[16,47].

Nucleated cells, such as monocytes and macrophages, have also been linked to the processes behind aspirin resistance in addition to platelets. In terms of their capacity for synthesis, these cells are second only to platelets in terms of TxA_2 availability[50]. These cells can renew the enzyme, nevertheless, in contrast to anucleate platelets. Prostaglandins are produced by this regenerated, unrestrained COX-1 in nucleated cells, which is then transferred to the platelets to make aspirin-insensitive/resistant thromboxane, avoiding platelet COX-1. These nucleated cells have the ability to produce their own TxA_2 in addition to that which is mediated by COX-1 through COX-2, which is not blocked by aspirin at low concentrations[19,30]. In contrast to constitutively expressed COX-1, inflammatory stimuli increase COX-2 expression in nucleated cells by a factor of 10–20[19,32]. These nucleated cells may activate platelets with the help of the TxA_2 they manufacture, starting a chain reaction50. There is evidence that atherosclerotic tissue has an upregulated level of COX-2. Aspirin resistance and acute coronary syndromes may result from the macrophages in the atherosclerotic plaque contributing considerably to the pool of TXA_2 that is not inhibited by modest dosages of aspirin[48]. Studies have demonstrated that erythrocytes can increase platelet reactivity and be prothrombotic. Not all individuals experience a consistent blocking of this cell-to-cell contact by aspirin, which might offer a different route for the development of thrombus [51].

The varying effects of aspirin in different persons may also be due to genetic variances. Firstly, a genetic foundation for aspirin resistance may be provided by polymorphisms or mutations of the COX-1 gene, which renders it relatively resistant to the action of aspirin. Single nucleotide polymorphisms (SNPs) of COX-1 may occur and influence an individual`s susceptibility to aspirin's inhibitory effect.117 SNPs are thought to act as mediators of phenotypic variation and provide the genetic foundation for a drug's variable response. Second, the variable effects of aspirin in different people may potentially be due to genetic variations in the glycoprotein IIb/IIIa receptor complex. The last common route for platelet activation is the glycoprotein IIb/IIIa receptor. The PIA_1 and PIA_2 alleles are defined by a common polymorphism involving the replacement of Leu33 for Pro, respectively. The majority of research show that PIA_3 carriers are less sensitive to aspirin`s antithrombotic actions and exhibit increased platelet activation by agonists, despite contradictory data. The amount to which the glycoprotein IIb/IIIa polymorphism influences aspirin`s functions contributes to both the drugs clinical effectiveness and resistance to its effects is still unknown, though.

Despite consistency of such observation, the prevalence of aspirin resistance has been variable in different populations and there is lack of standardized diagnostic criteria on a single validated method of identifying affected individuals to have aspirin resistance. It has led to wide range of population estimates[18]. Even though, aspirin resistance should be seriously considered in patients of IHD or stroke who are taking the prescribed dose regularly but getting recurrent coronary events or stroke. These patients need supplementation or supplant of other antiplatelet drugs. Unfortunately there are reports showing that clopidogrel, a thienopyridine derivative, commonly used as an antiplatelet agent, also demonstrates resistance in many patients.

CONCLUSION

The present study demonstrated that aspirin non-responsiveness in IHD patients living in and around Udaipur is 10%, of which 2% are having true resistance and 8% are semi-responders. The real prevalence in population around the study area is thought to be much more than reflected by the present study because the present study has excluded patients with diabetes, hypertension, history of smoking and female patients in whom incidence of aspirin resistance is reported to be high. Aspirin resistance or non-responsiveness is clinically important particularly in patients of recurrent infarction in whom chances of aspirin resistance are 40%. Aspirin resistance and duration of aspirin consumption have proportionate relation as majority of patients demonstrating aspirin resistance were consuming aspirin for more than 5 years. Further large scale study is warranted including different population with different disease using other parameters of assessment of platelet function.

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Research Paper

Role of Corticosteroids in Treatment of Neurotuberculosis

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ABSTRACT

A retrospective study showing a difference in neurotuberculosis patients receiving ATT and another group receiving ATT+ corticosteroids for 4-6 weeks in tapering doses was done in IPD patients of GBH General Hospital. The results were consistent with other authors that in patients receiving ATT+ steroids, the recovery was better & smooth without significant side effects.

KEYWORDS: Neurotuberculosis, Corticosteroids, Mycobacterium tuberculosis

INTRODUCTION

Neurotuberculosis is a common neurological disorder in developing countries. Among all patients of neurotuberculosis, tubercular meningitis is an important manifestation with high morbidity and mortality[4]. Diagnosis is based on clinical features, C.S.F. changes, & imaging. Polymerase chain reaction shows promise for the future. Appropriate chemotherapeutic agents should be given as early as possible. Role of corticosteroids is controversial but should be administered to all patients presenting in stage III[1]. Surgical procedures are directed only when, hydrocephalus, focal lesions, intracranial tuberculomas, and tuberculous abscesses, are located in cerebral or cerebellar hemispheres, uncommonly in brainstem and very rarely in spinal cord but usually surgical intervention is not required. Almost all patients respond well to medical management (ATT, ATT+Corticosteroids).

The patients who received ATT+ Steroids (oral steroids in tapering doses over a period of 4-6 weeks) showed early symptomatic & therapeutic response & the recovery was smooth over period[1].

Increasing prevalence of HIV infection, in today's scenario, in underdeveloped countries contributes to prevalence of Neurotuberculosis[4].Other important risk factors include over-crowding of urban population, poor nutritional status, appearance of drug-resistant strains of tuberculosis, ineffective tuberculosis control programmes, and increase in migration from countries where tuberculosis is prevalent to the developed world.

MATERIAL AND METHOD

The present study was carried out on 50 cases (35 males & 15 females) of various forms of neurotuberculosis, admitted in various wards of AIIMS Medical College and Hospital from a period of April 2017 to March 2022. Control subjects total 30 (15 males & 15 females) were in-patients with disorders other than tubercular neurological involvement.

Those patients were selected for studies that were having: -

1. Detection of antigen with clean specimens such as cerebrospinal and pleural fluids or

2. Detection of specific components of Mycobacterium tuberculosis by linked gas chromatography and mass spectroscopy or
3. Detection of specific DNA sequences of M. tuberculosis in specimens by use of labelled 'DNA sensitivity, by use of the polymerase chain reaction to amplify small amounts of the specific DNA.
4. ADENOSINE DEAMINASE (ADA): ADA is an important enzyme in purine metabolism; irreversibly deaminates adenosine to inosine. It is associated with lymphocytic proliferation and differentiation and is a marker of cell mediated immunity. Two isoforms ADA1 and ADA2 are known. ADA2 is the major contributor to the total ADA seen in TBM. Sensitivities and specificities range from 73-100% and 71-99% respectively.
5. RADIOLOGICAL EVALUATION: Every patient with TBM was evaluated with contrast enhanced CT/MRI before the start or within 1st 48 hr of treatment. An abnormality depends on the stage of the disease. Hydrocephalus (70-85%), basal meningeal enhancement (40%), infarction (15-30%), tuberculoma (5-10%)[4].

Other nonspecific indicators of tuberculosis were discarded (like bromide partition test)

Clear-cut diagnosed and primarily treated cases were selected for the study. All the patients admitted for any reason to ICU were NOT taken in this study.

RESULTS

Out of the 30 control individuals, the patients neither needed ATT, or ATT with steroids or steroids for any detectable reason. And these patients responded well to the specific treatment they were given for their respective illnesses other than tuberculosis.

In patients with neurotuberculosis, male & female patients didn't show any difference in treatment variability, with two different groups. One with ATT alone & another with ATT + steroids in routine standard doses (Dexamethasone 0.4mg/kg body weight IV during hospitalisation, followed by Prednisolone orally in doses of 1mg/Kg body weight, in tapering doses over a period of 4-6 weeks).

Table 1: Age at Presentation and Gender Distribution of Neurotuberculosis

SEX	MEAN AGE	RANGE	S D
MALE (35)	17.6	11-48.5	0.31
FEMALE (15)	15.4	10-45.1	0.23

Table 2: Student 'T' Test and 'P' Values for Two Types of Therapy

	ATT ONLY			ATT + STEROIDS		
	t	**df**	**p**	**t**	**df**	**p**
MALE NORMAL v/s PATIENTS	2.29	18	>0.51	7.63	18	>0.001
FEMALE NORMAL v/s PATIENTS	3.21	16	>0.60	7.81	16	>0.001

The survival rate was 100%, & none patient required ICU management. These patients were hospitalised for fairly enough time for symptomatic relief, and then followed initially fortnightly, then monthly till end of therapy, and finally all relevant investigation were performed to observe a satisfactory outcome before stopping their treatment & allowing them to live normal routine.

DISCUSSION

CNS tuberculosis is secondary to disease elsewhere in the body. Mycobacteria reach the brain by hematogenous route. The disease begins with the development of small tubercular foci (Rich foci) in the brain, spinal cord or meninges. According to British Tuberculosis Society and American Tuberculosis Society duration of treatment is 9-12 months. Ethambutol should be replaced by Streptomycin. Intensive phase (2 months) — Isoniazid, Rifampicin, Pyrazinamide and Streptomycin. Continuation phase (7-9 months) – Isoniazid and Rifampicin.

FIRST LINE ATT: Daily Dose in Children &Adults:

Isoniazid 10-20 mg/kg= 300 mg; Rifampicin 10-20 mg/kg =450mg (<50 kg) =600mg (>50 kg); Pyrazinamide 30-35 mg/kg =1500 mg (<50 kg) =2000 mg (>50 kg); Streptomycin 20-30 mg/kg. Isoniazid in doses of 15mg/kg penetrates the CSF freely and has potent early bactericidal activity. Resistance to Isoniazid develop quickly if used as a monotherapy. Rifampicin penetrates the CSF less well, but its key role in t/t of CNS tuberculosis is very well estabilished[4].

TNF alpha play a important role in pathogenesis and leads to altered blood brain barrier permeability and CSF leucocytosis.

The use of corticosteroids as adjunctive therapy in t/t of CNS tuberculosis begins as early as 1950[1]. It was proposed that steroids cause reduction of inflammation within subarachnoid space. It causes modulation of the local production of proinflammatory cytokines and chemokines by microglial cells. But the exact mechanism is not clear.

Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hr.IV during hospitalization,followed by prednisolone 1mg/kg bodyweight/day orally (after meals) with a tapering course over 6-8 weeks

High CSF ADA activity has been reported in patient with lymphoma, malaria, brucellosis, pyogenic meningitis and cerebral lymphoma.

The Infectious Disease Society of America, CDC and ATC recommend the use of Steroid therapy as an adjunctive therapy with standard anti tuberculosis therapy in CNS affection with mycobacterium[4].

SUMMARY

50 cases (35 male & 15 females) of neurotuberculosis (various forms), were subjected to ATT, ATT+steroids and studied along with 30 control hospitalised patients.

Our study shows close co-relation with other authors from India in treating uncomplicated various forms of neurotuberculosis, where additional benefit was found by adding steroids to ATT for initial 4-6 weeks, without causing any side-effects, except in special circumstances.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Case Report

Spontaneous Intracranial Bleed in a Young Non-hypertensive Patient of Neurofibromatosis Type 1

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ABSTRACT

Neurofibromatosis type 1(NF1), is an autosomal dominant inherited disorder characterized by numerous cutaneous neurofibromas, intertriginous freckling, dermal and plexiform neurofibromas and cafe-au-lait spots1.Cerebrovascular disease in the setting of NF 1 is a rare entity. Among the rare cerebrovascular abnormalities, the most common is occlusion of the small cerebral arteries leading to infarcts. Intracranial aneurysms are quite uncommon with only few cases reported worldwide. It is hypotheised that the pathogenesis may be attributable to the proliferation of Schwann cells and the subsequent degeneration in the adjoining vessel wall. We hereby report an uncommon case of NF1 associated with massive intracerebral haemorrhage most likely caused by vessel wall rupture.

KEYWORDS: Cafe-au-lait spots, Lisch nodule, Plexiform neurofibromas

CASE REPORT

A 44 year old normotensive and nondiabetic male patient diagnosed case of Neurofibromatosis type 1 presented in our casualty with sudden onset right sided weakness and speech difficulty associated with severe headache. On admission, the patient was fully conscious and oriented with motor weakness of right half of body and right-sided facial weakness. There was no history of similar event in past nor was any non modifiable risk factor for the same. No visual or sensory symptoms were present. Widespread cutaneous neurofibromas and angiomas were found along with axillary freckling and cafe –au-lait spots over trunk (Figure 1). Ophthalmological evaluation showed presence of Lisch nodules (Figure 2). Noncontrast CT of brain revealed a significant amount of bleed in left gangliocapsular region with slight oedema. Surprisingly the blood pressure and fundoscopy was also normal for the patient. He did have a family history of NF1 with his son also a diagnosed case of NF1 with Moya Moya disease. On subsequent investigations routine blood parameters were normal and further MR angiography of intracranial vessels revealed similar findings without any aneurysm or malformation. The patient was managed conservatively for the raised intracranial pressure and responded well to treatment. Neurodeficit improved partially with time and is still under follow up. MR angiogram did not reveal any intracranial aneurysm of blockage of arteries which leads us to a conclusion of source of bleed to be either a vascular malformation or episodic hypertensive bleed.

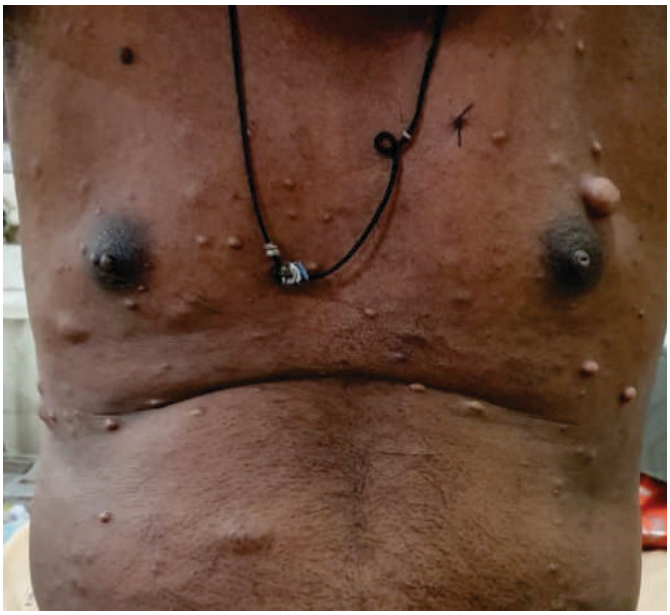

Figure 1: Multiple Neurofibromas and plexiform neuromas

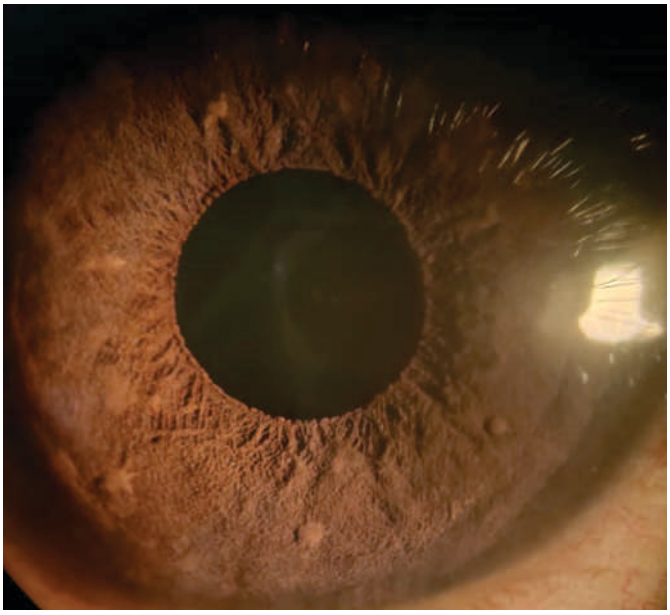

Figure 2: Lisch nodules over iris as seen on slit lamp examination

DISCUSSION

Neurofibromatosis type I (NF-1) is a complex multi-system disorder caused by the mutation of NF1 gene on chromosome 17 which is responsible for production of protein neurofibromin. NF-1 causes tumors of the nervous system which can grow anywhere in the body. It is an autosomal dominant disease and one of the most common mendelian disorders[2]. Clinical hallmarks include hamartomas on iris called as Lisch nodules, benign skin tumors called neurofibromas, multiple café au lait spots and large benign tumors of nerves called plexiform neurofibromas. Central nervous system symptoms include scoliosis, learning difficulties, visual symptoms and rarely seizures. NF-1 affected individuals also have a much higher incidence of

cardiovascular disease than the population in general. The three most common cardiovascular manifestations of NF1are vasculopathy, hypertension, and congenital heart defects[3].

The primary neurologic involvement in NF-1 is of the peripheral nervous system, and rarely that of the central nervous system. Sørensen *et al* found that cerebrovascular accidents often occurred at a younger mean age than other patient[4]. Hypertension is significantly associated with higher mortality, and the mean age of death among NF1 patients is almost 14 years younger than expected[5]. Cerebrovascular accidents in NF1 patients usually arise from occlusions of the internal carotid, middle, or anterior cerebral artery[6]. In rare incidences telangiectatic vessels form around the area of the stenosis and appear as a "puff of smoke" ("Moya-Moya") on cerebral angiography which is the case with the only child of this patient. Intracranial aneurysms and arteriovenous fistulae may also be seen in NF1 patients but are very rare and mostly in elderly population[7].

NF1 patients who present with a neurological deficit of sudden onset at any age should be evaluated promptly for cerebrovascular disease either occlusive of haemorrhagic. Cerebral angiography is appropriate when the history and Computed tomography is indicative of vascular lesion. It is noteworthy that many reported cases of neurofibromatosis with cerebral occlusive disease reveal stenotic or telangiectatic involvement of mostly middle or anterior cerebral arteries[8]. Some anecdotal reports also describe aneurismal bleeding in these patients[9]. Hypertension is a common cause of cerebrovascular mortality in NF1 patients but we could not find any evidence of high BP in this patient or any family history of same. This leads us to a conclusion of possibility of any vascular malformation or agenesis leading to deep cerebral bleed in this case. Treatment of in individuals with NF1 is identical to that in other CVApatients including both surgical and medical options. This opens up further possibilities of preliminary diagnostic screening in such patients to rule out any high risk lesion in both cardiovascular and cerebral vasculature and correction of the same medically or surgically.

CONCLUSION

Neurofibromatosis patient are prone to cerebrovascular complications in form of both vasoocclusion and parenchymal bleeding leading to neurodeficit or coma at a relatively young age. Active screening with neuro-imaging along with strict blood pressure monitoring should be the protocol to avoid morbidity and mortality in these patient groups.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Case Report

Formal Thought Disorder - A Case of Extra-ordinary Answers to Ordinary Questions

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ABSTRACT

Formal thought disorder (FTD) has been a subject of interest for phenomenologists for a long time. Ever since Bleuler introduced the concept of "loosening of associations," it has been recognized as a fundamental symptom of psychosis. The understanding of FTD has evolved over time, and we now know that it involves a range of cognitive and linguistic abnormalities. While it was originally believed to be exclusive to schizophrenia, it is now acknowledged that FTD can also occur in affective psychoses, non-psychotic disorders, and even in individuals without any psychiatric conditions. Despite some promising research findings about FTD, there is still a lot that remains unknown or undiscovered about this symptom. One of the challenges in studying FTD is its clinical diversity, as its core clinical characteristics have not been definitively established. This sparks interest in this case of a 45 year old woman presented with chief complaints of irrelevant and incoherent thought with marked disturbances in verbal communication that had typical markers of symptoms that characterise a disruption in the expression and organisation of ideas and thoughts.

KEYWORDS: Formal Thought Disorder, Schizophrenia, Cognitive disturbances

BACKGROUND

Formal thought disorder is a prominent psychopathological feature primarily associated with schizophrenia and related psychotic disorders, and denotes a disruption in the foundational cognitive processes that govern the coherent and logical expression of ideas[1]. Schizophrenia often impacts thought content, which might include auditory hallucinations and delusions, whereas FTD affects thought processes, such as how you structure sentences, choose speech, and formulate logical arguments.FTD is an objective sign indicative of schizophrenia psychopathology, which differentiates it from delusions and hallucinations, considered as diagnostic of schizophrenia, but found in many other psychiatric diagnoses. This disorder is marked by several key attributes.FTD rating scales describe up to eighteen distinct anomalies in speech rate and arrangement[2]. It is suggestive of a collection of linked affective, linguistic, and cognitive conditions. As a consequence, research on FTD has been explored from a variety of clinical viewpoints, encompassing psychiatry, neurolinguistics, and cognitive neuroscience.

Individuals grappling with FTD exhibit disorganized thinking, which impairs their ability to effectively structure and communicate their thoughts, resulting in speech and writing that appear disjointed and fragmented. Second commonly prevalent phenomenon is loose associations in thought, leading to responses or statements that lack logical

continuity with previous topics, rendering discourse incoherent. Thirdly, word salad may manifest as an extreme form, characterized by chaotic combinations of unrelated words and phrases, rendering communication unintelligible. Additionally, individuals may engage in clang associations, connecting words based on sound rather than meaning, further disrupting logical discourse. Finally, neologisms or unconventional word usage are common. Recognizing formal thought disorder is vital in clinical assessment and diagnosis due to its substantial impact on effective communication and conveying coherent ideas, making it a critical criterion for understanding and managing psychotic disorders in academic and clinical contexts[6].

It is strongly heritable with occurrences observed in unaffected relatives of individuals diagnosed with schizophrenia. Specifically, family members of those with schizophrenia exhibit specific traits, including reduced verbal fluency, distinctive word usage, unconventional verbal expression, and simplified grammar, when compared to individuals without the disorder[4]. Furthermore, studies involving adoptees, designed to minimize the impact of genetic and environmental factors, reveal that individuals with schizophrenia who were adopted tend to display significant FTD compared to adopted individuals without the condition. Similarly, biological relatives of adopted individuals with schizophrenia show a higher incidence of FTD than the biological relatives of adopted individuals without schizophrenia. These findings suggest that genetic factors play a substantial role in the susceptibility to schizophrenia, overshadowing the influence of early life experiences.

CASE PROFILE

The following excerpts summarise positive findings in a case of chronic psychotic illness, highlighting salient features suggestive of FTD in history and examination. A 45 year old female, belonging to lower socioeconomic background, living in a joint family from rural background was brought to us by her elderly parents with complaints of irrelevant, incomprehensible talks, difficulties with spoken communication, muttering and insomnia for a total duration of 7 years. The onset seemed to be insidious and course of symptom progression was continuous with predominant complaints of suspicion, remaining aloof, poor self care and aggression without provocation.

Parents reported that the patient had recently worsened. She was talking nonsensical words which were difficult to comprehend and largely irrelevant. The patient would frequently scream and cry loudly, while looking for a baby from the terrace of their house and saying that 'they' would take the baby and kill it. This was not in any context of recent pregnancy or childbirth. She had a history of infertility and had borne no children over 25 years of her married life.

After a recent event on the occasion of 'Janmashtami' she had started to behave as though she was Goddess 'Durga' and 'Kali' and would behave possessed by them. Her family sought faith healing and took her to an 'Ojha' (local shaman) to exorcise any evil spirit. However, the faith healer denied the role of any spirit and directed the family to visit a Mental Health Professional.

On examination, her first impressions included being agitated and vigilant. She was unable to provide appropriate answers. For example, if asked what her age is then she would reply 115 years. When asked about her siblings, she answered that she has 108 sisters and brothers. She would often include names of made-up places and people when asked open ended questions. She was persevering on the word 'Halwaai' and would keep circling back to this term. Her sentences also showed marked clang associations and rhyming words. For examples, when asked about her mother she says 'mummy nahi kami par zameenhai'.

She also talked about ideas such as 'my mother is a Goddess (Devi) and lives on the sun and can hear me from anywhere'. Another verbatim seen was 'my brother is an incarnation of the Pandavas', 'my father is a God who can control what goes on around him'. However this content of thought kept shifting. She would also sit idle for hours and smile inappropriately and often mutter to herself. Reduced psychomotor activity and inappropriate affect, incongruent to grandiose thought content were observed.

On treatment, she showed slow but consistent response, with improvement in affect appropriateness and reactivity, and reduction in content of grandiose thinking. Her answers were still largely irrelevant but more circumstantial than before. She was prescribed Tab. Olanzapine 10mg and Tab. Quetiapine 100mg daily in divided doses.

Thus, we could observe various signs of formal thought disorder such as loosening of associations or derailment, tangential thinking, word salad, perseveration, concreteness, and impaired communication in mental status examination[12]. This report intends to highlight the clinical presentation of the same in a patient of chronic psychotic illness.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Review

Inhibition of α-Amylase Enzyme Activity through Plants: A Promising Approach for Diabetes Management

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ABSTRACT

A class of metabolic disorders known as diabetes is referred by hyperglycemia brought on by abnormalities in insulin production. Postprandial hyperglycemia is ultimately caused by the breakdown of starch by α-amylase, which also generates glucose. One possible treatment strategy for diabetes mellitus involves blocking the α-amylase enzyme to reduce postprandial increase in blood glucose levels. Many of the anti-diabetic drugs such as voglibose, acarbose, and miglitol act as α- amylase inhibitors. Nevertheless, their costs are high and their applications come with unfavourable consequences. Several studies demonstrated the efficacy, safety, and acceptance of natural products and medicinal plants as useful sources of novel anti-diabetic medicines with a strong ability to suppress α-amylase enzyme activity. Therefore, an overview is conducted to find out the plants having in vitro α-amylase inhibitory activity. The analysis of the data reveals that several plant extracts have α-amylase inhibitory activity, which is quite comparable to the standard anti-diabetic drug. Notably, most of the studies have been carried out in recent years indicating the growing interest among researchers to find safer and more effective α-amylase inhibitors from plants.

KEYWORDS: DNSA test, Diabetes, Medicinal Plants, Phytochemicals, Natural products

INTRODUCTION

Diabetes mellitus, a metabolic disorder associated with chronic hyperglycemia, is one of the most common health problems in the world[1-3]. It is predicted[4-5] that it will impact around 800 million adults by 2045. The conditions that cause hyperglycemia include insulin resistance at the cellular level, a decrease in the function of the pancreatic beta cells that secrete insulin, and abnormal metabolism of proteins, lipids, and carbohydrates[6,7]. Diabetic patients suffer from additional conditions badly impacting their health for example, high blood pressure, persistent increase in systemic adrenergic activity, dyslipidemia etc. eventually leading towards organ failure or malfunction, especially in the kidneys, eyes, nerves, blood vessels, and heart[8-11].

Therefore, management of stable blood glucose is the only strategy that is successful in treating diabetes. In this context, inhibition of two digestive enzymes, namely, α-glucosidase and α-amylase is an important strategy[12]. These inhibitors alter the environment in the body such that there is a delay in breakdown of carbohydrates and the bloodstream's absorption which decreases the level of blood glucose generated after a meal[13,14].

The α-1,4-glucan-4-glucanohydrolases; known as α–amylase (E.C. 3.2.1.1) is an important enzyme used for carbohydrate digestion; especially glycogen and starch. This enzyme is not only present in microorganisms, but also in plants and higher organisms. It is present in pancreatic juice and saliva. α–amylase is a calcium metalloenzyme which functions as a catalyst and makes it easier for polysaccharide molecules like amylose, amylopectin, glycogen, and other maltodextrins to hydrolyze their α-1,4 glycosidic linkages[15]. Inhibition of this enzyme lowers down the carbohydrate digestion and thereby reduces the entry of carbohydrates into bloodstream. This is eventually helpful for diabetic patients. Moreover, inhibition of α–amylase is treated as a prophylactic treatment for high blood sugar levels[16,17].

Conventional anti-diabetic drugs such as miglitol, acarbose, and voglibose are effective against the α-amylase enzyme. However, due to the lack of specificity associated with these drugs, several unwanted gastrointestinal side effects, including cramps, stomach distention, flatulence, and diarrhoea, have been reported[18,19]. Therefore, the search for new α-amylase and α-glucosidase inhibitors is essential for the control of blood sugar in diabetes mellitus. Natural compounds are widely used for the production of novel medications and are increasingly being used to produce hypoglycemic agents[20-22]. Several *in vitro* investigations have shown the inhibitory effect of medicinal plants on the activities of α-amylase and α-glucosidase. These therapeutic actions are attributed to the secondary metabolites found in the plants[17,23,24]. The present review aims to investigate the potential therapeutic benefits of plants and their phytochemical constituents for the inhibition of α-amylase to treat Diabetes mellitus.

METHODOLOGY

An exhaustive literature search was carried out on the online databases such as Pubmed, Google Scholar, Scopus, Springer Link, Science Direct, and Research gate using the keywords, α-amylase, diabetes mellitus, inhibition, medicinal plants, plant extract, antidiabetic, *in vitro* etc. to find out the suitable references during the period of last 20 years *i.e.* from 2004 to 2023. The relevant papers were studied in detail and results of those studies as *in vitro* α-amylase inhibition property of plants is given below.

In vitro α-amylase inhibition

Some of the plants traditionally used for treatment of diabetes in Africa and Europe were screened for their *in vitro* α-amylase inhibition potential. A moderate inhibition activity (45-75%) was found in *Camellia sinensis, Khaya senegalensis, Melissae officinalis, Rosamarinus officinalis* and *Balanites aegyptiaca.* Leaves of *Vaccinium myrtillus* exhibited more than 75% inhibition. Leaves of *Mitragyna inermis* exhibited an inhibition of 75% whereas leaves of *Tamarindus indica* demonstrated 90% inhibition. The standard drug acarbose demonstrated 85% inhibition[25].

In vitro antidiabetic efficacy of hexane extract of *Phyllanthus amarus* was evaluated by Ali *et al*.[18] By extracting and fractionating the hexane extract of *P. amarus*, dotriacontanyl docosanoate, triacontanol, and a combination of oleanolic acid and ursolic acid were obtained. Every compound underwent the α-amylase inhibition experiment; the findings indicated that the oleanolic acid and ursolic acid (2:1) combination was a potent α-amylase inhibitor, with an IC_{50} value of 2.01 μg/mL. α-amylase was found to be inhibited by lupeol, ursolic acid, and oleanolic acid.

Bhandari *et al*.[26] investigated *in vitro* anti-diabetic efficacy and identified the active components from *Pakhanbhed* (*Bergenia ciliata*). Two active compounds, (−)-3-O-galloylepicatechin and (−)-3-O-galloylcatechin, were isolated for the first time from this plant species. Against rat intestinal porcine pancreatic α-amylase, these isolated compounds exhibited strong dose-dependent enzyme inhibitory action, with an IC_{50} value of 739 μM for [(−)-3-O-galloylepicatechin] and 401 μM for [(−)-3-O-galloylcatechin]. According to Loizzo *et al*.[27], the methanol extracts of *Marrubium radiatum* and *Salvia acetabulosa* exhibited the strongest activity against α-amylase, with IC_{50} values of 61.1 and 91.2 mg/mL, respectively.

Subramanian *et al*.[28] evaluated *in vitro* and *in vivo* antidiabetic activity of ethanolic extract of *Andrographis paniculata* and its bioactive molecule, andrographolide. The extract revealed significant *in vitro* α-amylase inhibitory effect in a concentration-dependent manner (IC_{50}= 50.9 ± 0.17 mg/mL). However, andrographolide displayed strong inhibitory activity (IC_{50}=11.3 ± 0.29 mg/mL). The *in vivo* investigations showed that when oral starch and sucrose administration was given to diabetic rats, *A. paniculata* extract considerably ($P<0.05$) decreased the animals' peak blood glucose and area under the curve and andrographolide also significantly ($P<0.05$) decreased the area under the curve and peak blood glucose in diabetic rats.

In vitro α-amylase inhibitory activity against porcine pancreatic amylase (PPA) was assessed by Tamil *et al*.[29] using three extracts of *Phyllanthus amarus*: ethanol, hexane, and chloroform. A rotary evaporator was used to evaporate the extracts under low pressure after they were prepared sequentially with chloroform, ethanol, and hexane. The extracts were produced at different concentrations (10, 20, 40, 60, 80, and 100 μg/mL) and then subjected to the α-amylase inhibitory experiment using dimethyl sulfoxide (DMSO) as the substrate. The absorbance was noted at 595 nm. The activity of α-amylase was not inhibited by the chloroform extract. However, in comparison to the standard drug acarbose (IC_{50} 83.33 ± 0.34 μg/mL), the hexane and ethanol of *P. amarus* shown substantial α-amylase inhibitory activity, with IC_{50} values of 48.92 ± 3.43 μg/mL and 36.05 ± 4.01 μg/mL, respectively. Veeramani *et al*.[30] reported *in vitro* α-amylase inhibitory potential of ethanolic flower and leaf extracts of *Catharanthus roseus* (Fig. 3) using DNSA test. The flower and leaf extracts displayed IC_{50} values of 12.5mg/mL and 10 mg/mL, respectively.

In vitro α-amylase inhibition of three distinct isopropanol extracts was investigated by Sudha *et al*.[31]. IC_{50} value of 540 µg/mL was obtained for *Linum usitatissumum* seeds, IC_{50} of 8.9 µg/mL for *Ocimum tenuiflorum* leaves, and IC_{50} of 1440 µg/mL for *Morus alba* was observed. Acarbose, the reference drug, showed an IC_{50} value of 10.2 µg/mL.

Saha and Verma[32] evaluated the α-amylase inhibition test to determine the *in vitro* antidiabetic activity of three different plants: *Eugenia cumini* (seeds), *Terminalia arjuna* (stem bark), and leaves of *Aegle marmelos* (Fig. 1). Fifty percent methanolic extracts of *A. marmelos*, *E. cumini*, and *T. arjuna* showed α-amylase inhibitory action at 50-500 µg/mL concentrations, with IC_{50} values of 503 ± 0.28 µg/mL, 632 ± 0.21 µg/mL, and 302 ± 0.55 µg/mL, respectively. However, the lowest levels of inhibitory action were shown by the 100% methanol extracts of all the three plants.

Kazeem *et al*.[33] demonstrated *in vitro* α-amylase inhibitory activity of different extracts of *Morinda lucida*. Aqueous extract revealed the maximum α-amylase inhibitory with IC_{50} value of 2.30 mg/mL, when compared with ethanolic and acetone extracts. The n-hexane fraction obtained from hydro-methanolic (2:3) extract of *Salmalia malabarica* (Fig. 2) sepals revealed α-amylase inhibition with the IC_{50} value of 50.17 mg/L whereas the standard drug acarbose revealed an IC_{50}value of 47.19 µg/ml[34].

Prabhakar *et al*.[35] investigated *in vitro* α-amylase inhibitory efficacy of aqueous and methanolic extracts of different medicinal plants. The highest percentage of α-amylase inhibition was found in the aqueous extract of *Withania somnifera* (Fig. 4) leaves (92.7%) and the methanolic extract of *Ocimum sanctum* leaves (92.6%) followed by the methanolic bark extract of *Azadirachta indica* (91%), the aqueous extracts of *Curcuma longa* (90.9%), *O. sanctum* (90.3%), and the methanolic leaf extract of *A. indica* (90%). The extracts with the lowest levels of α-amylase inhibition were the methanolic extract of *W. somnifera* (65.1%) and the aqueous bark extract of *A. indica* (77%). *In vitro* α-amylase inhibitory activity of ethanolic extract of *Senna surattensis* (IC_{50} value 123.95 µg/mL) was studied by Thilagam *et al.*[36] using 3,5-Dinitrosalicylic acid assay (DNSA).

The butanolic extract of *Zhumeria majdae* was examined by Mirshafie *et al*.[37] for α-amylase inhibition at different concentrations (15-30 mg/mL), using acarbose as standard. The α-amylase enzyme was inhibited in a dose-dependent fashion by the butanol extract. The extract inhibited activity of the enzyme by 77.9 ± 2.1% at 30 mg/mL, while acarbose inhibited enzyme activity by 73.9 ± 1.9% at 20 mg/mL. IC_{50} values were found to be 24.5 ± 2.1 mg/mL and 6.6 ± 3.1 mg/mL for the butanol extract and acarbose, respectively.

Afrisham *et al*.[38] used the DNSA approach to test the *in vitro* α-amylase inhibitory effect of *Heracleum persicum* and *Ziziphus jujuba*. In comparison to the reference drug, acarbose (IC_{50} of 113µg/mL), the methanolic extracts of *Z. jujuba* and *H. persicum* demonstrated strong inhibitory efficacy against α-amylase, with IC_{50} values of 867µg/mL and 307µg/mL, respectively.

Poovitha and Parani[39] performed the DNSA test to inhibit the α-amylase enzyme to examine the possible antidiabetic properties of protein extracts from the fruits of two different types of bitter gourd (*Momordica charantia* L.). It was discovered that the α-amylase activity was inhibited in a dose-dependent manner between 0.5 and 2.5 mg/mL by *Momordica charantia* var. *charantia* (MCC), *Momordica charantia* var. *muricata* (MCM), and acarbose protein extracts. The highest inhibition of α-amylase activity by protein extracts from MCC, MCM, and acarbose was 66.5%, 67.0%, and 68.0% at a concentration of 2.5 mg/mL, respectively. The protein extracts of MCC, MCM, and acarbose have shown IC_{50} values of 0.267 ±0.024, 0.261 ±0.019, and 0.258 ±0.017 mg/mL, respectively.

Wickramaratne *et al*.[40] analysed *in vitro* α-amylase inhibitory potential of various extracts of leaves of *Adenanthera pavonina* employing DNSA method. The IC_{50} values of water, petroleum ether, ethanol and methanol extracts were found as 214.85 ± 9.72, 145.49 ± 4.86, 59.93 ± 0.25 and 16.16 ± 2.23 µg/mL, respectively and whereas the standard drug acarbose exhibited an IC_{50} value of 18.63 ± 1.21 µg/mL.

Jaiswal and Kumar[41] reported *in vitro* α-amylase inhibition potential of bark of *Albizia lebbeck* (L.) Benth. The maximum enzyme inhibition (43.50±0.17% to 73.43±0.08%) was showed by free flavonoid extract with IC_{50} value 0.6653 mg/mL followed by water, methanol and bound flavonoid extracts *i.e*., 26.67±0.12% to 32.07±0.17%, 26.70±0.15 to 32.67±0 .12% and 28.63±0.15% to 37.50±0.20%, with IC_{50} value of 22.28 mg/mL, 41.68 mg/mL and 7.36 mg/mL, respectively.

Bhosale *et al*.[42] screened *in vitro* α-amylase inhibitory activity of aqueous extracts of five plants *viz*., leaves and rhizome of *Curcuma longa* and leaves of *Azadirachta indica*, *Moringa oleifera*, *Murraya koenigii* (Fig. 5) and *Psidium guajava* using DNSA assay. Highest α-amylase inhibition activity was revealed by aqueous extract of leaves of *C. longa* with IC_{50} values of 0.53±0.10 followed by rhizome of *C. longa* 0.96±0.29, leaves of *Moringa oleifera* 1.24 ± 0.49, leaves of *Azadirachta indica* 1.54 ± 0.59, leaves of *Murraya koenigii* 1.57 ± 0.76 and leaves of *Psidium guajava* 4.50 ± 0.38 mg/mL, respectively in comparison with the standard drug acarbose having an IC_{50} value of 0.15 ± 0.11 mg/mL.

The antidiabetic efficacy of *Wedelia chinensis* methanolic extract was assessed by Thao *et al*.[43]. A bioactive compound jaceosidin had the strongest effect on α-amylase, with an IC_{50} value of 112.8 ± 15.1 µg/mL, and was found quite similar to acarbose, which had an IC_{50} value of 124.0 ± 21.3 µg/mL. Nevertheless, wednenic, pomonic, and pomolic acid showed a modest level of inhibition against α-amylase. Unuofin *et al*.[44] evaluated *in vitro* α-amylase inhibitory activity of aqueous and ethanol extracts of tuber of *Kedrostis africana* (L.) Cogn using the starch iodine assay and found the inhibition in a dose-dependent manner. At the concentrations 50, 100, and 200 µg/mL, aqueous and ethanol extracts exhibited inhibition

of 19.85 ± 0.37% to 31.64 ± 1.11% and 13.91 ± 1.55% to 20.14 ± 0.63%, respectively. However, the positive control acarbose revealed 92.98 ± 1.37% inhibition at 64 µg/mL. The IC_{50} values were 439.45 ± 1.95 and 949.75 ± 3.68 µg/mL for aqueous and ethanol extracts, respectively.

Ahmed *et al*.[45] reported *in vitro* α-amylase inhibitory property of miquelianin from *Euphorbia schimperi* with an IC_{50} value of 128.34 ± 12.30 µg/mL, and acarbose revealed IC_{50} value 64.20 ± 5.60 µg/mL. Methanolic stem bark extracts of *Maesobotrya dusenii* was evaluated by Mikailu *et al*.[46] for α-amylase inhibition activity. The extract exhibited a dose-dependent inhibition of α-amylase, even though the percentage of the standard drug, acarbose, was greater at 64 percent than that of crude methanol at 56.7% at 50 µg/mL. The methanol extract and acarbose were found to have IC_{50} values of 24 and 28µg/mL, respectively. *In vitro* and *in vivo* antidiabetic effects of *Terfezia claveryi* methanol extract were evaluated by AlAhmed and Khalil[47]. *T. claveryi* extract demonstrated a greater α-amylase inhibitory activity (IC_{50} = 38.7 µg/ml) than the positive control (IC_{50} value = 45.3 µg/ml) of acarbose. Moreover, the *T. claveryi* methanol extract, at a dosage of 200 mg/kg, also lowered the fasting plasma glucose level in the animal study.

The *in vitro* antidiabetic potential of three distinct extracts of leaves, stem bark, and root bark of *Alstonia boonei* was examined by Oyebode *et al*.[48]. The α-amylase enzyme was shown to be effectively inhibited by all of the extracts. However, ethanol extracts of leaves, stem bark, and root bark, demonstrated significant ($p < 0.05$) inhibition with IC_{50} values of 102.93, 16.78, and 129.06 µg/mL, respectively.

Hawash *et al*.[49] reported *in vitro* α-amylase inhibitory activities of hydrophilic and lipophilic fractions of leaves of *Arum palaestinum*, *Malva sylvestris, Plantago major*, *Centaurea iberica, Cichorium endivia, Bituminaria bituminosa* and *Sisymbrium irio*. The highest enzyme inhibition activity was found in lipophilic fractions of *S. irio* with an IC_{50} value of 7.72 µg/mL, followed by hydrophilic fraction of *C. endivia* (9.96 µg/mL). However, positive control, acarbose revealed an IC_{50} value of 10 µg/mL. The hydrophilic fractions of leaves of *P. major, M. sylvestris, A. palaestinum, S. irio, B. bituminosa and C. iberica* inhibited α-amylase with IC_{50} values of 352.31, 38.55, 573.72, 180.43, 180.43 and 12.33 µg/mL, respectively. The lipophilic fractions of leaves of *P. major, A. palaestinum, C. endivia,* and *B. bituminosa* inhibited the enzyme with IC_{50} values of 61.35, 25.34, 300.92, and 529.49 µg/mL, respectively.

The *in vitro* anti-α-amylase activity of different fractions of *Prosopis cineraria* pod extract was assessed by Kumar *et al*.[50]. The most effective fraction to inhibit α-amylase was n-butanol (IC_{50} 22.01 ± 0.92 µg/mL) followed by ethyl acetate fraction (IC_{50} of 28.23 ± 1.06 µg/mL). However, the IC_{50} of acarbose, the reference drug, was 39.26 ± 2.19 µg/mL. The *in vitro* α-amylase inhibition potential of leaf latex of *Aloe megalacantha* Baker and leaf of *Aloe monticola* Reynolds were examined using DNSA method. The IC_{50} values found for *A. megalacantha* and *A. monticola* were 74.76 ± 1.98 and 78.10 ± 1.88 µg/mL, respectively against the α-amylase. Acarbose, the standard drug, revealed an IC_{50} value of 16.49 ± 1.91 µg/mL[51].

Nine plants were evaluated for α-amylase inhibitory action by Hussein *et al*.[52]. With the highest percentage of inhibition (95.5%), *Raphanus raphanistrum* was found to be the most effective among them. Other plants that showed the highest percentage of inhibition were *Citrus limon*, *Matricaria chamomilla*, *Punica granatum*, *Allium sativum*, *Syzigium aromaticum*, *Zingiber officinale*, *Beta vulgaris* and *Nigella sativa* with corresponding inhibition percentages of 87.3, 83.5, 81, 72, 66.6, 60.6, 59.4 and 9.0.

Khadayat *et al*.[53] demonstrated α-amylase inhibition potential of *Swertia chirata*, *Dioscorea bulbifera,* and *Acacia catechu* with IC_{50} values 413.5, 296.1, and 49.9 µg/mL, respectively. However, the standard drug acarbose exhibited an IC_{50} value 6.1 µg/mL. Two triterpenes, namely, 3-oxolupenal and katononic acid were isolated from n-hexane fraction of the methanolic crude extract of *Nuxia oppositifolia* and evaluated for *in vitro* α-amylase inhibitory potential. The IC_{50} values of 46.2 µg/mL and 52.4 µg/mL were observed for 3-oxolupenal and katononic acid, respectively in comparison with control acarbose having IC_{50}of27.3 µg/mL[54].

According to Gök *et al*.[55], ethyl acetate extract of *Rhus coriaria* L. leaf inhibited α-amylase *in vitro* with an IC_{50} value of 20.810 ± 0.747 µg/mL, while acarbose showed an IC_{50} value of 26.993 ± 0.797 µg/mL. Notably, a bioactive compound, penta-*O*-galloyl-β-glucopyranose isolated from both fruit and leaf extracts of *R. coriaria* inhibited α-amylase with an IC_{50} value of 6.32 ± 0.18 µM. Hoang Anh *et al*.[56] demonstrated the α-amylase inhibitory property of *Clausena indica* fruits. The hexane and ethyl acetate extracts inhibited the α-amylase with IC_{50} values of 1.37 ± 0.01 and 8.56 ± 0.24 mg/mL, respectively. Remarkably, α-amylase suppression by acarbose was having an IC_{50} value of 0.07 ± 0.00 mg/mL. Jaradat *et al*.[57] reported that the acetone extract of *Nonea obtusifolia* leaves had a more effective α-amylase inhibitory effect when compared to acarbose, with IC_{50} values of 25.7 ± 0.08 µg/mL and 28.18 ± 1.22 µg/mL, respectively.

Kirisanth *et al*.[58] investigated *in vitro* α-amylase inhibitory activities of six different bryophyte species *viz*. *Calymperes motley*, *Fissidens* sp., *Hypnum cupressiforme*, *Marchantia* sp., *Plagiochila* sp. and *Sematophyllum demissum* using DNSA method. The ethyl acetate extract of *Fissidens* sp. exhibited the maximum inhibitory activity (39%) followed by *Marchantia* sp. (23%), *Plagiochila* sp. (12%) and *H. cupressiforme* (8%). However, positive control acarbose had shown 66% inhibitory activity. *C. motley* and *S. demissum* were found inactive for α-amylase inhibition activity.

Pandey *et al*.[59] evaluated *in vitro* α-amylase inhibitory activity of different extracts of *Bergenia pacumbis* using DNSA method. The methanol extract revealed the highest inhibition (IC_{50} = 14.03 ± 0.04 µg/mL) followed by ethyl acetate extract (29.91 ± 0.22 µg/mL), and water (43.77 ± 0.54 µg/mL). Acarbose, a standard drug showed an IC_{50} value of

20.12 ± 0.12 µg/mL.

Panigrahy *et al.*[60] evaluated *Hedychium coronarium* rhizome for α-amylase inhibition potential. The ethyl acetate fraction of rhizome inhibited α-amylase activity with IC_{50} value of 58.15 ± 1.23 µg/mL. The hypoglycemic properties of *Melilotus officinalis* and *Anchusa officinalis* were assessed by Paun *et al.*[61]. The highest α-amylase inhibitory activity was found in the crude extract of *M. officinalis* (IC_{50} = 1.32 ± 0.08 µg/mL), followed by that of *A. officinalis* (954.16 ± 7.46 µg/mL). However, the IC_{50} value of acarbose was 17.68 ± 1.24 µg/mL.

Momina and Rani[62] evaluated *in vitro* α-amylase inhibitory activity of methanolic leaf extracts of *Bambusa vulgaris*, *Lindernia ciliata* and *Phyllanthus reticulatus* (Fig. 6). At a concentration of 10mg/mL the methanolic extracts of *B. vulgaris*, *L. ciliata*, *P. reticulatus* and acarbose exhibited 69.5%, 83.1%, 72% and 97.3% α-amylase inhibitory activity, respectively. Among all the extracts, *L. ciliata* revealed significant α-amylase inhibition activity with IC_{50} 6.11 mg/mL which was quite comparable with an IC_{50} value of 5.03 mg/mL revealed by the standard drug acarbose. Quek *et al.*[63] investigated *in vitro* α-amylase inhibitory activity of different extracts of stem bark and leaves of *Melicope glabra*. The chloroform extract of leaves was obtained to be the most effective towards inhibition of α-amylase with IC_{50} of 303.64 µg/mL followed by chloroform extract of stem bark IC_{50} 975.80 ± 17.10, methanol leaves IC_{50} 2488.13 ± 231.54, methanol stem bark IC_{50} 3946.12 ± 143.21, hexane leaves IC_{50} 4230.12 ± 324.76, and hexane stem bark extracts IC_{50} 5447.01 ± 243.16 µg/mL.

Eriobotrya japonica leaves were tested for their *in vitro* antidiabetic potential by Mogole *et al.*[64]. Various extracts were tested against the activity of α-amylase, with acarbose serving as the control. Hexane extract had the greatest α-amylase inhibitory activity of 24% at a concentration of 1 µg/mL when compared to other extracts. *In vitro* α-amylase inhibitory activity of methanol extracts of *Oroxylum indicum* leaf (OIME) and *Rauvolfia tetraphylla* root (RTME) was shown by Swargiary and Daimari[65]. At a dose of 2 mg/mL of the extracts, the percent inhibitions for OIME, RTME, and acarbose were reported as 70.96%, 38.50%, and 59.80%, respectively.

Daoudi *et al.*[66] examined the α-amylase inhibitory effect of roasted (Roil) and unroasted (UnRoil) *Argania spinosa* seed oil *in vitro*, *in vivo*, and *in situ*. The findings demonstrated that, *in vitro*, pancreatic α-amylase was considerably ($p < 0.001$) inhibited by both Roil and UnRoil, with IC_{50} values of 2.17 ± 0.24 mg/mL and 0.78 ± 0.16 mg/mL, respectively. These were found quite comparable with acarbose (0.41 ± 0.015 mg/mL). Moreover, oral administration of these oils at a dosage of 2 mL/Kg reduced blood sugar in normal and STZ-diabetic rats.

Thengyai *et al.*[67] reported α-amylase inhibitory potential of the ethanol extract of the stem bark of *Vitex glabrata.* Six bioactive compounds *viz.,* α-amyrin, *β*-amyrin, betulin, betulinic acid, lupeol, and scopoletin *were isolated from V. glabrata stem bark* and the maximum α-amylase inhibitory activity was observed by *β*-amyrin (IC_{50} 32.33 µM). Rocamora *et al.*[68] reported *in vitro* α-amylase inhibition of essential oil derived from leaves of *Backhousia citriodora, Mentha piperita, Origanum vulgare,* and *Rosmarinus officinalis.* Inhibition of α-amylase found by *Mentha piperita* was (IC_{50} 0.41 mg/mL) followed by *Origanum vulgare* (IC_{50} 0.41 mg/mL), *Rosmarinus officinalis (IC_{50} 0.45 mg/mL),* and *Backhousia citriodora* (IC_{50} 0.49 mg/mL).

Anigboro *et al.*[69] examined *in vitro* α-amylase inhibitory activity of leaf extract of *Justicia carnea* using DNSA method. A dose-dependent significant ($p<0.05$) reduction in α-Amylase activity (IC_{50} value 671.43±1.88 µg/mL) was exhibited by leaf extract. The IC_{50} value of standard acarbose was found to be 108.91±0.61 µg/mL. Quek *et al.*[70] reported α-amylase inhibitory activity of different extracts of *Melicope latifolia* bark. The maximum inhibition was revealed by chloroform extract with IC_{50} value of 1464.32 ± 312.19 µg/mL followed by methanol extract (2941.17 ± 113.72 µg/mL) and hexane extract (8113.15 ± 103.15 µg/mL).

Renganathan *et al.*[71] demonstrated *in vitro* antidiabetic potential of 70% ethanolic leaf extract of *Leucaena leucocephala* (Lam.) De Wit. The leaf extract inhibited α-amylase activity in a concentration-dependent way (IC_{50} = 288.01 µg/mL), while acarbose inhibited α-amylase with an IC_{50} value of 252.59 µg/mL. Choudhary *et al.*[72] analysed *in vitro* α-amylase inhibitory activity of various fractions of *Chenopodium album* L. The aerial parts of *C. album* were fractionated into different fractions, *i.e.,* alkaloid fraction (CAAF), flavonoid fraction (CAFF), saponin fraction (CASF) and tannin fraction (CATF). The *in vitro* assay revealed that CAFF was found to be more significant α-amylase inhibitory than the reference drug acarbose having IC_{50} values of 122.18 ± 1.15 and 812.83± 1.07 µg/mL, respectively. *In vivo* antidiabetic potential was screened using a high-fat diet and streptozotocin-induced diabetic mice. In both *in vitro* and *in vivo* diabetes models, the CAFF fraction was reported to have strong antidiabetic efficacy in a dose-dependent manner. On days 22 and 29, the levels of plasma glucose, total cholesterol, and total triglycerides were compared. The rise in glucose, cholesterol, and triglyceride levels, were reduced significantly after seven days administration of CAFF fraction at a dose of 500 mg/kg.

Abolaji *et al.*[73] examined *in vitro* antidiabetic potential of acetone extract of *Ziziphus mucronata* (AEZM) through determination of its α-amylase inhibition potential. The extract exhibited a dose-dependent rise in α-amylase inhibition. At a concentration of 1.0 mg/mL, AEZM and the standard drug, voglibose revealed (71.02%) and (83.47%) inhibition, respectively. Additionally, IC_{50} values for AEZM and voglibose were found as 0.62 and 0.42 mg/mL, respectively.

Methanolic extract of aerial parts of Phragmites *karka* was investigated for antidiabetic potential through α-amylase inhibition by Mazumder *et al.*[74]. Using the iodine starch and DNSA techniques, a significant inhibition of the enzyme was

shown in the α-amylase enzyme inhibitory test, with IC_{50} values of 2.05 and 2.08 mg/mL, respectively. Sani *et al*.[75] evaluated the α-amylase inhibitory activity of *Arachis hypogaea* and *Cinnamomum tamala*. The ethanol extract from peanut (*A. hypogaea*) seeds demonstrated α-amylase inhibition activity (67.68±8.67%) at 1.25 µg/mL concentration, with an IC_{50} value of 0.61µg/mL. This is extremely near to the standard α-amylase inhibitor acarbose (72.34±4.23%) with an IC_{50} value of 0.32 µg/mL. Similarly, the acetone extract from Indian bay (*C. tamala*) leaf showed α-amylase inhibition activity (47.75±1.63%) at 1.42 µg/mL at the same concentration.

Sen *et al*.[76] reported *in vitro* α-amylase inhibitory activity of the essential oil obtained from the aerial parts of *Centaurea pterocaula* Trautv. An IC_{50} value of 79.66 ±0.43 µg/mL was found for α-amylase inhibition. However, the standard drug acarbose had an IC_{50} value of 11.6 ± 0.18 µg/mL. Silva *et al*.[77] reported *in vitro* α-amylase inhibition of hexane fraction from Brazilian *Morus nigra* leaves. The α-amylase inhibitory activity of hexane fraction was found with an IC_{50} value of 13.05 mg/mL whereas acarbose had an IC_{50} value of 0.21 mg/mL.

Saraswathi *et al*.[78] evaluated *in vitro* α-amylase inhibition of aqueous and ethanolic and aqueous extracts of *Solanum virginianum* dried fruits at different doses (20–120 µg/mL). In a concentration-dependent manner, the aqueous extract (54.12 ± 0.44–86.80 ± 0.27%) showed a considerably ($P<0.05$) greater rate of α-amylase inhibition than the ethanolic extract (23.07 ± 0.47–81.61 ± 0.43%). At all the doses, α-amylase was considerably ($P<0.05$) more inhibited by standard drug acarbose (58.36 ± 0.30–88.24 ± 0.16%) rather than by aqueous and ethanolic extracts. According to Prasathkumar *et al*.[79], methanolic extract of *Senna auriculata* (L.) Roxb. leaves showed α-amylase inhibition with an IC_{50} value of 49.45 µg/mL.

Yashoda *et al*.[80] investigated the ability of methanolic extracts of *Achyranthes aspera* and *Catharanthus roseus* to inhibit the α-amylase enzyme using DNSA test. The inhibition of α-amylase by *A. aspera* and *C. roseus* was determined to be 97.60±1.11 µg/mL and 94.05±1.18 µg/mL, respectively, in comparison to the IC_{50} of 68.13±0.46 µg/mL of reference drug acarbose. Bello *et al*.[81] observed that the *Eucalyptus globulus* plant's both leaf DEE ethanol extract (hexane defatted) and NEE ethanol extract (non-defatted) exhibited α-amylase inhibitory action. When compared to acarbose, the extracts showed a discernible suppression of α-amylase. The α-amylase inhibition IC_{50} values for DEE, NEE, and acarbose were 23.6 ± 1.2 µg/mL, 14.8 ± 1.2 µg/mL, and 5.2 ± 1.3 µg/mL, respectively.

In vitro α-amylase inhibitory activity of crude methanolic extract of *Pastinaca sativa* (CEPS) was determined by starch iodine test. IC_{50} values for CEPS and acarbose were found as 91.69 ± 1.5 µg/mL and 83.25 ± 1.28 µg/mL, respectively. CEPS also exhibited *in vivo* blood sugar lowering effect in alloxan-induced diabetic rats. Blood glucose levels decreased from 208.33 mg/dL to 106.38 mg/dL and from 209.82 mg/dL to 111.65 mg/dL after administration of 200 and 400 mg/kg CEPS, respectively. These results were comparable to standard drug glibenclamide (0.5 mg/kg) which exhibited a significant drop from 205.55 mg/dL to 84.88 mg/dL on the seventh day[82].

Mechchate *et al*.[83] observed that the hydroethanolic leaf extract of *Withania frutescens* L. significantly inhibited α-amylase in dose-dependent manner. Notably, the plant extract (IC_{50} 0.40 ± 0.124 mg/mL) demonstrated higher *in vitro* α-amylase inhibition as compared to acarbose (0.717 ± 0.054 mg/mL). The ethanolic extract of *Moringa oleifera* flower demonstrated a significant ($p < 0.05$) dose-dependent inhibition against α-amylase (IC_{50} = 37.63 mg/mL) as compared to the standard drug acarbose[84]. Shanak *et al*.[85] reported α-amylase inhibitory potential of methanolic extract of aerial parts of *Ocimum basilicum*. A 500 µg/mL concentration, the plant extract demonstrated 25.4% ± 3.3 α-amylase inhibition.

Siegień *et al*.[86] screened α-amylase inhibitory potential of aqueous and ethanolic extracts of twelve plants *viz*., *Hibiscus sabdariffa, Chaenomeles japonica, Hippophae rhamnoides, Berberis vulgaris, Rosa canina, Quercus spp., Sorbus aucuparia, Juglans regia, Sambucus nigra, Aronia melanocarpa, Artemisia dracunculus,* and *Humulus lupulus. H. sabdariffa* flower revealed the highest inhibitory activity of α-amylase with IC_{50} values of 35.81 ± 3.660 and 40.22 ± 2.898 µg/mL for aqueous and ethanolic extracts, respectively followed by *C. japonica* fruit aqueous extract (53.61 ± 5.074) and ethanolic extract (48.69 ± 4.993), *H. rhamnoides* fruit aqueous extract (83.01 ± 7.840) and ethanolic extract (92.99 ± 7.804), *B. vulgaris* fruit aqueous extract (252.9 ± 27.59) and ethanolic extract (378.0 ± 44.94), *R. canina* fruit aqueous extract (823.3 ± 107.6) and ethanolic extract (401.9 ± 71.97), *Quercus* spp. fruit aqueous extract (1123 ± 133.3) and ethanolic extract (1550 ± 129.7), *S. aucuparia* fruit aqueous extract (1236 ± 177.0) and ethanolic extract (973.9 ± 61.60), *J.regia* fruit aqueous extract (1479 ± 183.6) and ethanolic extract (295.0 ± 74.04), *S. nigra* fruit aqueous extract (2091 ± 160.1) and ethanolic extract (2259 ± 344.4), *A. melanocarpa* fruit aqueous extract (2632 ± 208.5) and ethanolic extract (1130 ± 91.19), *A. dracunculus* herb aqueous extract (6778 ± 405.4) and ethanolic extract (2824 ± 273.0) and *H. lupulus* flower aqueous extract (9249 ± 525.0) and ethanolic extract (7215 ± 784.7) µg/mL. However, IC_{50} for the reference drug was found as 2.4 ± 0.4 µg/mL.

In vitro α-amylase inhibitory activity of *Catunaregam spinosa* leaf and bark methanol extracts was conducted by Timalsina *et al*.[87]. The α-amylase inhibitory activity of the bark methanol extract was also evaluated for the hexane, dichloromethane, ethyl acetate, and water-soluble fractions. The IC_{50} value of the crude bark extract (94.66 ± 2.19 µg/mL) was lower than that of the crude leaf methanolic extract (119.7 ± 2.79 µg/mL), suggesting that the former was more potent. The ethyl acetate and dichloromethane fractions exhibited IC_{50} values 116 ± 1.60 and 77.17 ± 1.75 and µg/mL, respectively whereas the standard acarbose revealed an IC_{50} of

6.34 ± 0.07 µg/mL.

Bakshi *et al*.[88] screened *in vitro* α-amylase inhibitory potential of methanol extracts of *Azadirachta indica*, *Bauhinia variegata*, *Dalbergia sissoo*, *Psidium guajava*, and *Syzygium cumini* leaves. Notably, *S. cumini* and *B. variegata* exhibited strong inhibitory effects against α-amylase with IC_{50} values of 24.69 ± 0.91and 27.28 ± 6.11 µg/mL, respectively.

Acetone extracts of *Artemisia pallens* Wall ex DC. leaf and bud were evaluated for their *in vitro* α-amylase inhibitory action[89]. The extract efficiently suppressed PPA with an IC_{50} of 388.05 µg/mL, while acarbose, a positive control and known inhibitor of pancreatic amylase, had an IC_{50} of 9.71 µg/mL. The plant extract at increasing concentration of 62.5 µg/mL, 125 µg/mL, 187.5 µg/mL, 250 µg/mL, and 312.5 µg/mL demonstrated 28.36%, 35.05%, 38.93%, 43.45%, and 46.19% inhibitory activity in an increasing manner.

Dar *et al*.[90] examined the α-amylase inhibitory activity of the methanolic heartwood extract of *Pterocarpus marsupium* (MHPM). A strong dose-dependent α-amylase inhibitory action was shown by MHPM, with an average inhibition of 66.441 ± 3.459% at 500 µg/mL and an IC_{50} value of 158.663 ± 10.986 µg/mL. At 500 µg/mL, the percentage inhibition of the positive control, acarbose, was 78.410 ± 4.005%, while the IC_{50} value was 56.060 ± 4.465 µg/mL.

Hassan *et al*.[91] evaluated *in vitro α*-amylase inhibition activity of various extracts of *Veronica biloba*. Water extract showed highest inhibition with IC_{50} value of 110.25 *µ*g/mL, followed by ethyl acetate 121.09, dichloromethane 123.68, and n-hexane 148.01 *µ*g/mL extracts. Interestingly, acarbose had an *α*-amylase inhibition activity with IC_{50} value of 138.79*µ*g/mL However, the bound phenolics of *V. biloba* revealed IC_{50} = 219.66 *µ*g/mL.

Karray *et al*.[92] demonstrated *in vitro* α-amylase inhibitory activity of different extracts of *Moringa oleifera* leaf. The methanol extract disclosed the highest α-amylase inhibitory activity (65.6 ± 4.93%), followed by hexane extract (52.3 ± 2.5%). The extracts of water, ethylene acetate, and ethanol showed much lower amylase inhibitory activity, with inhibition rates of 43.3 ± 2.3%, 36 ± 2.6%, and 33 ± 2.6%, respectively. Olaokun *et al*.[93] reported *in vitro* hypogylcemic effect of *Englerophytum magalismontanum.* The crude methanol extract displayed an IC_{50} value 16.16 ± 2.23 µg/mL, while the methanol fraction and standard acarbose revealed $IC_{50\ of}$ 10.76 ± 1.33 and 1.24 ± 1.64 µg/mL. α-Amylase was inhibited by the phenolic compound that was extracted and identified as naringenin, with an IC_{50} of 5.81 ± 2.14 µg/mL. The methanolic leaf extract of *Morus alba* exhibited a dose-dependent α-amylase inhibition (78.55 ± 2.53%) at a dose of 500 µg/mL and an IC_{50} of 74.76 ± 6.76 µg/mL. Nonetheless, at 500 µg/mL, acarbose had 87.67 ± 3.67% inhibition, and the IC_{50} was 35.34 ± 4.87 µg/mL[94].

Prakash[95] examined the potential inhibitory effects of leaf extracts from *Rhododendron arboreum* and *Rhododendron campanulatum* on porcine α-amylase, with concentrations ranging from 0.2 to 1.0 mg/mL. At a dose of 1 mg/mL, *R. arboreum* showed 51.10, 44.00, and 35.40% inhibition for methanol, acetone, and aqueous leaf extracts, respectively. In similar dose of 1 mg/mL, *R. campanulatum* demonstrated α-amylase inhibition of 21.15, 18.25, and 15.85% for methanol, acetone, and aqueous extracts, respectively. Ahmed *et al*.[96] 2022 investigated *in vitro* anti-diabetic activity of *Calligonum polygonoides*; an important desert shrub of Rajasthan. They observed that 80% methanolic extract of *C. polygonoides* whole plant inhibited α-amylase by 70% at a concentration of 1 mg/ml with an IC_{50} of 610 µg/ml However, the standard tagipmet showed an IC_{50} of 424 µg/ml.

Benrahou *et al*.[97] evaluated *in vitro* and *in vivo* α-amylase inhibitory activity of different extracts of *Erodium guttatum.* All three extracts exhibited significant inhibitory impact ($P < 0.05$) on α-amylase, with the methanolic extract of *E. guttatum* exhibiting the strongest effect, showing an IC_{50} of 479.20 ± 0.81 µg/mL. The IC_{50} values of the aqueous and ethanolic extracts were 781.30 ± 0.54 and 498.5 ± 0.81 µg/mL, respectively. Acarbose, the positive control, revealed an IC_{50} of 44.75 ± 0.54 µg/mL. Blood sugar levels were reported to be affected by *E. guttatum* extracts and metformin. The diabetic mice treated with the three extracts plus metformin showed significantly different blood sugar levels on day one compared to the diabetic mice in the normal group who were not treated ($P < 0.05$). Conversely, there was no discernible difference ($P>0.05$) between the groups receiving metformin plus plant extract treatment and the diabetic group receiving no treatment. The results showed that blood sugar levels were considerably lower in the group of diabetic mice treated with *E. guttatum* extracts plus metformin after 30 days ($P < 0.05$).

Shreya Reddy *et al*.[98] reported *in vitro* α-amylase inhibitory ability of ethanolic extracts of *Andrographis paniculata* and *Andrographis echioides*. In a dose-dependent manner (100-500µg/mL), both the extracts significantly ($p<0.05$) increased the α-amylase inhibitory activity. By inhibiting α-amylase *in vitro*, Nisar *et al*.[99] evaluated the antidiabetic effect of *Picrorhiza kurroa* roots. The highest inhibitory activity of root against the α-amylase enzyme was shown by the methanol extract, with an IC_{50} value of 0.39 ± 0.41 mg/mL. Ethanolic and aqueous extracts trailed methanolic extract in terms of highest inhibitory efficacy against α-amylase. The *in vitro* α-amylase inhibitory activity of the ethyl acetate fraction of *Erythropalum scandens* was examined by Adhikari *et al*.[100] showing an IC_{50} value of 44.51 ± 0.12 µg/mL.

Das *et al*.[101] evaluated *in vitro* antidiabetic potential of ethanolic extract of *Coscinium fenestratum* (Gaertn.) Colebr seeds through DNSA method by inhibiting *α*-amylase activity. The percentages of enzyme inhibition activity were found to be 19.46%, 38.19%, 52.09%, and 61.22% at doses of 100, 200, 300, and 400 µg/mL, respectively. For the reference drug, acarbose at the same doses, higher activity was observed (36.11%, 52.10%, 64.28%, and 76.2%). The IC_{50} values for the seed extract and standard were determined to be 3.02 and 1.96 µg/mL, respectively. Interestingly, both the

extract and the standard showed a dose-dependent inhibition of *α*-amylase.

Mariadoss *et al*.[102] investigated the α-amylase inhibitory activity of *Lespedeza cuneata* fractions in methanol, ethyl acetate, and hexane solvents. With an IC_{50} of 205.32 ± 23.47 µg/mL, the ethyl acetate fraction of *L. cuneata* (Lc-EAF) demonstrated the most high α-amylase inhibitory activity among them. An *in vivo* study revealed that administering 100 mg/kg of Lc-EAF maintained blood glucose levels, decreased insulin levels, and enhanced the lipid profile, hepatic, and renal indicators in streptozotocin-induced diabetic rats. Recently, Omar *et al*.[103] have shown that methanolic extract of *Phyllanthus emblica* L. leaves possess significant α-amylase inhibition activity (98.37 ±1.09%).

In vitro α-amylase inhibitory effect of methanol extract of *Phoenix pusilla* ripened fruits (PPRF) was reported by Srinivasan *et al*.[104] on porcine pancreatic α-amylase having an IC_{50} value of 69.86 µg/mL. Ullah *et al*.[105] assessed the *in vitro* α-amylase inhibitory activity of ethanol and aqueous extracts of the seed, root, stem, flower, and gum, of *Acacia modesta*. When the Starch-iodine test was used, the aqueous extract of gum showed the highest inhibitory potential against α-amylase with an IC_{50} value of 91.8 ±0.05 µg/mL. This was nearly three times more than that of the control, acarbose (286.8 ± 0.04 µg/mL). In addition, the gum's ethanolic extract demonstrated strong activity, with an IC_{50} value of 100.4 ± 0.04 µg/mL.

The hypoglycemic effectiveness of raspberry (*Rubus corchorifolius* L.) leaf was reported by Li *et al*.[106]. Using affinity ultra filtration in conjunction with HPLC-MS/MS, eight major bioactive chemicals were identified, including epigallocatechin gallate, delphinidin-3-O-glucoside, cyanidin-3-rutinoside, isoorientin, procyanidin C3, dihydromyricetin, rutin, and isovitexin. Confirmation tests revealed that these compounds were in-charge of α-amylase's inhibitory actions. According to molecular docking studies, it was found that through hydrogen bonding or van der Waals force, these inhibitors may effectively interact with α-amylase. Different leaf extracts were evaluated *in vitro* for their potential to inhibit α-amylase. The extracts with the highest inhibiting activity were 70% ethanol (IC_{50} = 1.26 ± 0.03 mg/mL) and 70% methanol (IC_{50} = 1.47 ± 0.05 mg/mL) followed by aqueous extracts (IC_{50} = 4.39 ± 0.17 mg/mL). The positive control acarbose revealed an IC_{50} of 5.12 ± 0.42 mg/mL. Notably, the extracts of ethyl acetate and acetone showed poor inhibitory action (IC_{50} > 20.00 mg/mL).

Remok *et al*.[107] performed *in vitro* α-amylase inhibitory ability of aqueous extract of *Salvia lavandulifolia* Vahl leaf with an IC_{50} value of 0.99 ± 0.00 mg/mL which was found comparable with the standard drug, acarbose (IC_{50} = 0.52 ± 0.01 mg/mL). Yang *et al*.[108] analysed 16 phenolic compounds found in the ethyl acetate fraction of *Sterculia nobilis* Smith pericarp extract (EAF) using the LC-ESI-MS/MS-MRM technology. Apigegetrin, epicatechin gallate, and luteolin-7-O-glucoside were the main phenolics in the EAF. EAF exhibited reversible and uncompetitive inhibition of α-amylase activity, with an IC_{50} value of 2.151 ± 0.044 mg/mL.

CONCLUSION

Inhibition of alpha-amylase enzyme is a promising strategy towards management of high blood glucose in diabetes mellitus. The present review indicates the therapeutic potential of several plant species through inhibition of alpha-amylase activity and suggests the possibility of developing cheaper and safer plant-derived novel hypoglycaemic molecules. Interestingly, several of these studied plants are used in food for example, *Aegle marmelos, Allium sativum*, *Murraya koenigii, Curcuma longa, Citrus limon*, *Punica granatum*, *Zingiber officinale*, *Phyllanthus emblica, Momordica charantia, Eugenia cumini, Syzigium aromaticum, Moringa oleifera, Psidium guajava, Tamarindus indica, Ziziphus jujuba* etc. This further opens up the avenue for development of some nutraceuticals effective for the treatment of diabetes.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

Figure 1: *Aegle marmelos*

Figure 2: *Bombax ceiba*

Figure 3: *Catharanthus roseus*

Figure 4: *Withania somnifera*

Figure 5: *Murraya koenigii*

Figure 6: *Phyllanthus reticulatus*

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Review

Translational Research in Psychiatric Medicine: Bridging the Gap between Discovery and Patient Care

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ABSTRACT

This review delves into the transformative realm of translational research in psychiatric medicine, acting as the critical conduit between laboratory discoveries and practical applications in clinical settings. Employing a multidisciplinary approach, this process fosters collaboration among researchers, clinicians, and stakeholders to address the intricate complexities of mental health disorders. Emphasizing the significance of translational research, we explore its role in translating genetic insights and neurobiological discoveries into targeted interventions, ultimately enhancing patient care and treatment outcomes. Real-world applications are illuminated through examples, showcasing the tangible impact of translational efforts on treatment protocols. By addressing treatment gaps and tailoring interventions based on individual characteristics, this review underscores the shift toward personalized, patient-centered psychiatric care. Through collaboration and innovation, translational research emerges as a beacon, guiding the trajectory of psychiatric medicine toward a future defined by effective, tailored interventions for those navigating the challenges of mental health.

KEYWORDS: Translational research, Psychiatric medicine, Multidisciplinary approach, Laboratory discoveries, clinical applications, Mental health disorders

INTRODUCTION

Translational research in psychiatric medicine serves as the crucial bridge between fundamental scientific discoveries and their practical application in clinical settings. It encompasses the process of translating laboratory findings into tangible advancements that directly impact patient care and treatment outcomes. This multidisciplinary approach aims to address the complex nature of mental health disorders by fostering collaboration between researchers, clinicians, and other stakeholders[1]. The significance of translational research lies in its ability to transform theoretical knowledge gained from laboratory studies into innovative therapies, diagnostic tools, and preventive strategies[2]. By bridging the gap between the bench (where fundamental research occurs) and the bedside (where patients receive care), translational research ensures that scientific advancements are not confined to academic realms but actively contribute to improving the lives of individuals grappling with psychiatric conditions[3].

Neurobiological Discoveries

In recent years, neurobiological research has witnessed groundbreaking discoveries that hold profound implications for our understanding of mental health disorders. Advances in imaging techniques, genetic studies, and molecular biology have shed light on the intricate mechanisms underlying psychiatric conditions[4]. These breakthroughs offer new perspectives on the biological underpinnings of disorders such as depression, schizophrenia, bipolar disorder, and anxiety[5].

Studies exploring brain structure have revealed anomalies in specific regions associated with mood regulation, cognitive function, and emotional processing. Functional neuroimaging has provided insights into the dynamic interplay of neural circuits implicated in psychiatric disorders[6]. Additionally, research into neurotransmitter

systems, including serotonin, dopamine, and glutamate, has deepened our understanding of the chemical signaling disruptions that contribute to mental health challenges.By delving into these neurobiological discoveries, researchers and clinicians alike gain valuable insights that can inform the development of targeted interventions and personalized treatment approaches[7].

Genetic Insights

Genetic factors play a pivotal role in the susceptibility to psychiatric disorders[8]. Recent advancements in genetic research have uncovered a complex interplay between genetic predisposition and environmental factors, contributing to the manifestation of conditions such as schizophrenia, bipolar disorder, and major depressive disorder[9]. Through large-scale genome-wide association studies (GWAS) and advancements in molecular genetics, researchers have identified specific genetic variations associated with increased vulnerability to these disorders. The translation of genetic discoveries into psychiatric care involves the development of innovative diagnostic and therapeutic approaches[10]. Genetic biomarkers are increasingly being utilized for early detection and risk assessment. Moreover, pharmacogenomics, a field at the intersection of genetics and psychopharmacology, aims to tailor medication regimens based on an individual's genetic profile, optimizing treatment efficacy and minimizing adverse effects[11]. As we delve into these genetic insights, it becomes evident that the era of precision psychiatry is dawning, offering personalized interventions for those grappling with mental health challenges.

Innovations in Psychopharmacology:

Psychopharmacology, the study of drugs that affect the mind and behavior, is a rapidly evolving field with a rich history of innovation. In recent years, there have been a number of exciting breakthroughs in psychopharmacology that have the potential to revolutionize the treatment of mental health disorders.

Psychedelic renaissance

One of the most significant developments in psychopharmacology has been the resurgence of interest in psychedelic drugs, such as psilocybin and MDMA. These drugs have been shown to be effective in treating a variety of mental health conditions, including depression, anxiety, and post-traumatic stress disorder (PTSD)[12]. Psychedelic drugs are thought to work by increasing neuroplasticity, the brain's ability to form new connections. This can lead to new insights and perspectives, as well as a decrease in symptoms[13].

Novel antidepressants

In addition to psychedelic drugs, there have been a number of promising new antidepressants developed in recent years. These drugs, such as ketamine and esketamine, work differently from traditional antidepressants and have been shown to be effective in treating patients with treatment-resistant depression[14]. Ketamine and esketamine are thought to work by blocking the NMDA receptor, a protein that plays a role in mood regulation[15].

Targeting Neurobiological Mechanisms:

These advancements in psychopharmacology are characterized by a shift toward targeted interventions. Medications are designed to modulate specific neurobiological mechanisms implicated in psychiatric disorders[16]. For instance, drugs may act on the serotonin or dopamine systems to regulate mood or target glutamatergic pathways to address cognitive symptoms. Understanding the neurobiological underpinnings of mental health conditions enables the development of more precise and effective medications, bringing us closer to the goal of personalized treatment strategies[17].

Neuromodulation therapies

Neuromodulation therapies, such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), are also becoming increasingly common in the treatment of mental health disorders. These therapies use non-invasive or minimally invasive procedures to stimulate or inhibit specific brain regions. Neuromodulation therapies have been shown to be effective in treating a variety of conditions, including depression, anxiety, and obsessive-compulsive disorder (OCD)[18].

Digital therapeutics

Digital therapeutics is also being used to improve psychopharmacological treatment. These are apps, games, or other digital products that can be used to deliver therapy, track symptoms, and provide support. Digital therapeutics has the potential to make treatment more accessible and affordable, and to provide patients with more personalized care[19].

Personalized Medicine in Psychiatry

Psychopharmacology is also moving towards a more personalized approach to treatment. This means that treatment is tailored to the individual patient's needs and takes into account their genetic makeup, biological markers, and past treatment history[20]. Personalized medicine has the potential to improve treatment outcomes and reduce side effects. Personalized medicine in psychiatry represents a paradigm shift from the traditional one-size-fits-all approach to a more individualized and targeted model of care[21]. It involves tailoring psychiatric treatment strategies based on an individual's unique biological, genetic, and clinical characteristics. By integrating information from various sources, including genetic profiling, neuroimaging, and psychosocial factors, clinicians can develop more precise and effective interventions[16].

Highlighting the Potential for Tailoring Interventions:

The potential for tailoring interventions in psychiatry is vast. Genetic markers can guide medication selection and dosage, minimizing adverse effects and optimizing treatment response[22]. Neuroimaging data can inform the choice of therapeutic approaches by identifying specific neural circuits that may be dysregulated[23]. Moreover, considering an individual's psychosocial context allows for a holistic understanding of their mental health, paving the way for personalized psychotherapeutic strategies. The synthesis of these factors offers a comprehensive approach to psychiatric care, aligning treatments with the unique characteristics of each patient.

Challenges and Future Directions

While translational psychiatry holds great promise, it is not without challenges. The translation of research findings into clinical practice faces obstacles such as the complexity of mental health disorders, heterogeneity within patient populations, and the need for interdisciplinary collaboration.

Bridging the gap between basic research and clinical application requires overcoming barriers related to funding, data integration, and the integration of technological advancements into routine practice.To address these challenges, ongoing and future research in translational psychiatry is focusing on innovative methodologies and technologies. Multimodal approaches, combining genetic, neurobiological, and clinical data, aim to create comprehensive models that capture the intricacies of psychiatric conditions. Advances in artificial intelligence and machine learning are being explored to analyze large datasets and uncover patterns that may elude traditional methods. Furthermore, longitudinal studies tracking the trajectory of mental health disorders and treatment outcomes contribute to a deeper understanding of the dynamic nature of psychiatric conditions.

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Review

A Scopic Review on Reactive Thrombocytosis

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ABSTRACT

Thrombocytosis, also called thrombocythemia, is generally defined as platelet count greater than a defined upper limit of normal. The most common cut off for normal is <450,000/µl. Elevated platelet counts are often an incidental or unexpected finding on a complete blood count conducted to evaluate an unrelated condition. The causes of thrombocytosis are separated into two categories: autonomous (primary) thrombocytosis and reactive (secondary) thrombocytosis. Autonomous thrombocytosis occurs as a result of myeloproliferative disorders, myelodysplastic disorders, or rarely as a result of a hereditary condition. Reactive thrombocytosis is most often a normal physiologic response to coexistent chronic inflammatory conditions. Distinction between these two categories is important since autonomous thrombocytosis is associated with a significantly increased risk for thrombotic or hemorrhagic complications whereas reactive thrombocytosis is not. The most common reason for an elevated platelet count is reactive thrombocytosis. The present review will discuss about the association of reactive thrombocytosis with different clinical conditions and the possible underlying mechanism.

KEYWORDS: Thrombocythemia, Autonomous thrombocytosis, Platelet granules

INTRODUCTION

Historical Aspect - Discovery of Platelet

Brewer traced the history of the discovery of the platelet[1]. Although red blood cells had been known since van Leeuwenhoek (1632–1723), it was the German anatomist Max Schultze (1825–1874) who first offered a description of the platelet in his newly-founded journal Archiv für mikroscopische Anatomie[2]. Max Schultze describes "spherules" to be much smaller than red blood cells that are occasionally clumped and may participate in collections of fibrous material. He recommends further study of the findings.

Giulio Bizzozero (1846–1901), building on Schultze's findings, used "living circulation" to study blood cells of amphibians microscopically in vivo. He is especially noted for discovering that platelets clump at the site of blood vessel injury, a process that precedes the formation of a blood clot. This observation confirmed the role of platelets in coagulation[3].

PLATELET[4]

Platelets have been described as the smallest cell fragment in the human body[5] (Jurk & Kichrel, 2005). The normal platelets are small, disc-shaped cells without a nucleus, normally measuring 1 to 2 µm in diameter and 0.5 to 1.0 µm in thickness with a volume of about 6µl. Platelets are derived from the cytoplasm of megakaryocyte, primarily located in the bone marrow. Normally, a platelet is released to the blood stream and circulates for about 10 days before its removal, largely by the spleen. Platelets circulate freely without adhesion to the vessel wall or aggregation with other platelets. If stimulated, platelets become spherical, extend pseudo pods, and adhere to vessel walls and to each other. It participates with the blood vessel, coagulation factors, and other platelets in the initiation of haemostasis.

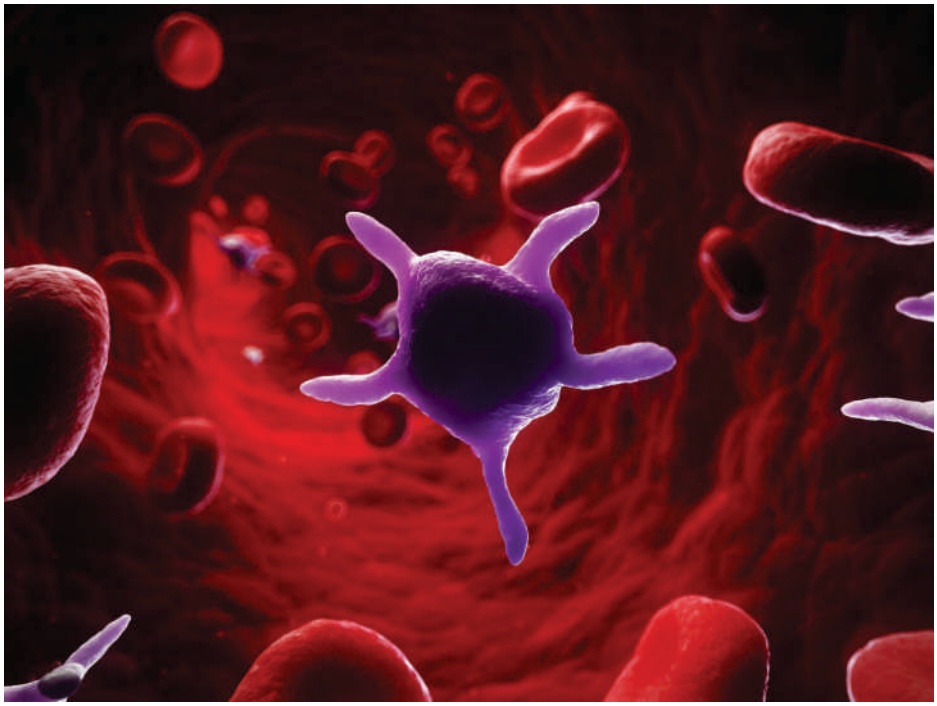

Figure 1: Platelet

Platelet Production and Release[4]

The megakaryocyte, parent cell of the platelet, is derived from pluripotential cells in the bone marrow. Individual megakaryocyte have been estimated to produce as many as 1000 platelets per cell, and apparently very efficient system facilitated by the absence of nuclei in platelets. IL-6 and IL-11 are thought to increase platelet production by megakaryocyte. There are two possible mechanisms whereby platelet achieves the transition from being stationary constituents of megakaryocyte cytoplasm in the bone marrow to circulation cells in the bloodstream. One theory is that megakaryocyte themselves are released from the bone marrow and are carried to the pulmonary capillaries, where they fragment into individual platelet. Another is that the bone marrow endothelium has special properties that encourage formation of pseudopods extending from mature megakaryocyte to bone marrow sinuses and thereby directly release platelets into the blood.

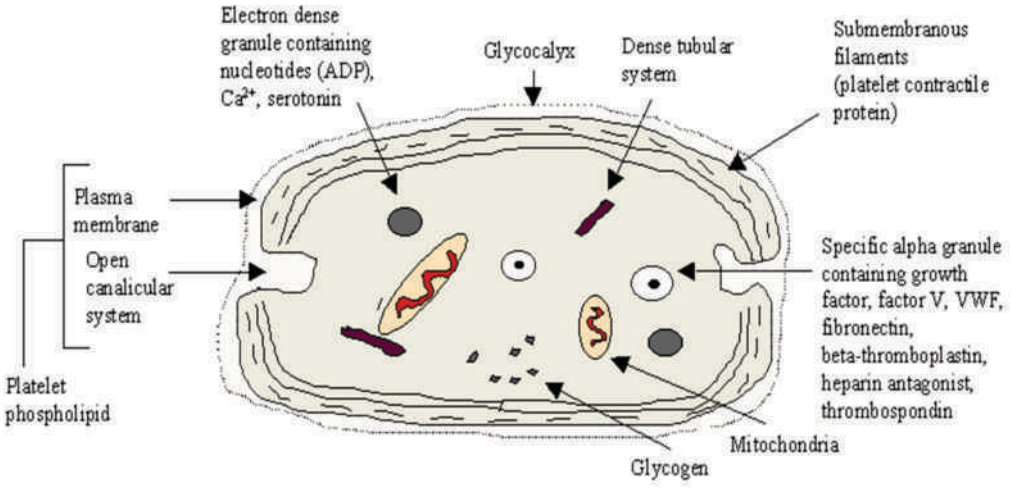

Figure 2: Ultra Structure of Platelet

Platelet Structure[4]

Platelets are composed of three principal components: membrane structures, microtubules, and granules. Platelet membrane, overlying glycocalyx, and submembrane structures mediate responses to platelet stimulation and express specific antigenic characteristics. The surface glycoprotein's variously serve as receptors, facilitate platelet adhesion, contraction, and determine expression of specific platelet antigens. Platelet canalicular system is created by numerous invaginations of the platelet surface and, interspersed among these structures; a set of narrower channels termed the dense tubular system. The canalicular system provides a direct connection between the interior and the surface of the platelet, providing entrance of plasma ingredients into the platelet as well as exit of its own ingredients in connection with the release reaction. The dense tubular system, on the other hand, is entirely enclosed and is the major site for storage of Ca^{2+} and the location of cyclooxygenase, the critical enzyme for conversion of membrane-derived arachidonic acid to unstable endoperoxide precursors of prostaglandins and thromboxanes. The major inner structures of the platelet are the cytoskeleton, the microtubules, and a system of contractile proteins. The cytoskeleton provides a framework to anchor the platelet membrane and allow signal transduction to take place. Furthermore, it is a framework against which the contractile proteins of the platelet can operate to initiate shape change and protrusion of pseudopodia at the onset of spreading. Actin, actin-binding protein, talin, vinculin, stectrin, a-actinin, and several membrane glycoproteins make up the cytoskeleton. Actin-binding protein binds both actin and GPIb-IX. In resting platelet this maintains the discoid shape of the platelet. With activation and calcium influx, calpain is activated, severing the link of actin-binding protein to GPIb-IX. The microtubules are arranged in the form of an inner ring beneath the surface of the platelet and are distinct from the canalicular and dense tubular systems of the membrane zone. The microtubules provide structural support of the platelet, maintain its discoid shape in the resting state, and influence the character of its contractile functions. Contractile proteins largely consist of myosin and submembrane actin filaments that are anchored to the surface of the platelet by the Tran membrane glycoprotein a-actinin. On stimulation of the platelet, the cytoplasmic concentration of Ca^{2+} rises and calmodulin is activated and combines with myosin light-chain kinase; this enzyme phosphorylates myosin, leading to the combination of myosin with actin to form contractile act myosin, which mediates the initial changes in shape of the platelet and ultimately, retraction of the formed clot.

The three types of storage granules dominate the central cytoplasm are the dense granules, alpha granules and lysosomal granules.

In general, platelet aggregation is associated with release but at least in vitro certain "strong" agonists, i.e., collagen and thrombin, can trigger release without aggregation. P selectin or GMP140 is a component of the a-granule membrane. Release involves the granules nearest the platelet surface being transported to the platelet membrane and fusing with it so that a

Content of Platelet Granules[6]

Dense Granules	Alpha Granules	Lysosomal Granules
Adenosine triphosphate	PF-4	Galactosidase
Adenosine diphosphate	Beta-thromboglobulin	Fucosidase
Glucuronidase	Fibrinogen	Hexaminidase
Calcium	Factor V	Thrombospondin
Serotonin	Fibronectin	Cathepsin
Pyrophosphate	Plasma inhibitors	
P-selectin(CD-62)	P-selectin(CD-62)	
Transforming growth factor beta-1	Platelet derived growth factor inhibitor(PDGF)	
Catecholamines	Alpha-2 macroglobulin	
Nor-adrenaline/adrenaline		
Guanosoine-5diphosphate		
GDP/guanosine-5(GTP)		
Triphosphate		

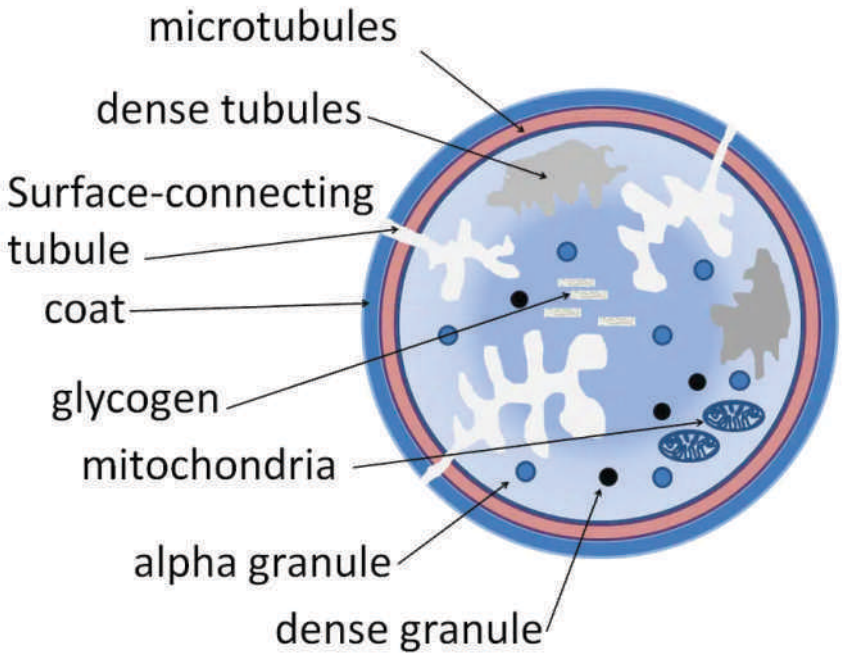

Figure 3: Platelet Structure

small portion of the post release external platelet membrane is made up of the inner membrane of theca-granule, including GMP140.

Dense bodies are granules characterized by high electron density and are fewer in number than a-granules. These structures serve as a depot for non-metabolic substances that are extrinsic to the platelet and may be picked up or released as indicated. On their release, these substances are particularly critical to platelet aggregation.

Lysosomal granules are also present in platelets, perhaps representing the original role of the platelet as a white blood cell. These granules contain at least seven acid hydrolyses. These enzymes may contribute to the intracellular effects of phagocytosis of may create an uncertain amount of damage extracellularly at the site of platelet release.

The contents and functions of the non-granular organelles of the platelet may be summarized as follows: mitochondria contain enzymes for oxidative metabolism and thereby provide a major source of energy through the generation of ATP, and peroxisomes contain catalase, which protects the platelet from oxidative damage in connection with periodically intense metabolic activity. Platelets also contain occasional ribosomal particles and small amounts of RNA.

On films made from blood anticoagulated with the strong calcium chelating agent ethylenediamine tetra acetic acid (EDTA) and stained with Wright's stain, platelet appears as small bluish-gray, oval-to-round with several purple-red granules. When anticoagulated blood is used to prepare blood films, platelet undergo variable activation and spreading and thus platelet aggregate are commonly seen: platelet from specimens may demonstrate three to four very long and thin processes extending out from the body of the platelet (filopodia).

Normal Range, Life Span and Physiological Variation of Platelet Count

The platelet count in the peripheral blood is maintained at a fairly constant level, which is in the range 150,000 to 450,000/cmm of blood in normal subjects. A somewhat lower range is seen in the newborn, normal adult level being achieved by about 3 months. Considerable fluctuation may occur during the course of menstrual cycle, lowest level being found at or just prior to menstruation. Heavy exercise and adrenergic stimulation tends to increase the platelet count transiently, possibly by mobilization of the splenic pool. There are some racial differences in platelet count for e.g. Mediterranean races' platelet count is as low as 80,000/ cmm of blood are sometimes found in normal individuals.

However in such cases the mean platelet volume is increased so that over all platelet mass is unaltered. Apart from this so called "Mediterranean Macrothrombocytopenia"[13] which is not clinically significant. There may be sex difference: thus in women, the platelet count have been reported to be about 2% higher than man. There is no evidence that oral contraceptives affect the platelet count. There are some ethnic differences and in healthy west Indians and Africans platelet counts may on average be 10-20% lower than those of Europeans living in the same environment. Strenuous exercise causes a 30-40% increase in platelet count. The normal life span of platelet ranges between 8 to 14 days[7].

Platelet Morphology and Number in Peripheral Blood Smear

Platelet appears in normal stained blood as small blue or colourless bodies with red or purple granules. Normal platelet average about 1-3 micrometer in diameter but show wide variation in shape, from round to elongated, cigar shaped forms. A rough estimate of the platelet count can be made by observation of the stained blood film. If the platelet count is normal, approximately 8 to15 platelet (individual or in small clumps) should be visible in each oil immersion field. There should be one platelet for every 10-30 erythrocytes[8].

The occurrence of giant platelets or platelet masses may indicate a myeloproliferative disorder, or absence of the spleen or improper collection of blood sample. Estimation of platelet concentration is best determined from EDTA anticoagulated blood, where the platelets generally do not aggregate[8].

Giant platelets and abnormal platelet granulation are characteristic features of idiopathic myelofibrosis[9].

Platelet morphology show large, pale-staining, hypo-granular platelet in essential thrombocythemia in peripheral smear. Characteristic morphological platelet features are seen in two platelet inherited disorders associated with bleeding. The Bernard- Soulier syndrome in which there are giant platelet with defective ristocetin response and Gray Platelet syndrome in which platelet lacks granules and have ghost like appearance on blood stained film[10]. In about 1% of patient EDTA anticoagulated blood causes platelet clumping and thus resulting in pseudo-thrombocytopenia.

Role of Platelet in Infection and Inflammation

Blood platelets are presented as active players in antimicrobial host defence and induction of inflammation and tissue repair in addition to their participation in hemostasis. Megakaryopoesis is inhibited after the acute infection with viruses or bacteria. In addition chronic inflammation is often associated with reactive thrombocytosis. Platelets can bind and internalize pathogens and release microbicidal proteins that kill certain bacteria and fungi. By making cell-cell contacts with leukocytes and endothelial cells, platelets assist white blood cells in rolling, arrest and transmigration. On stimulation by bacteria or thrombin, platelets release the content of their alpha granules, which include an arsenal of bioactive peptides, such as growth factors for endothelial cells, smooth muscle cells and fibroblast. This integral to innate immunity, the tiny little platelets may become bombshells when irritated by pathogens[11].

Thrombocytosis

Thrombocytosis is the presence of an abnormally high number of platelets in the circulating blood. It may result from various physiological stimuli and pathological processes[12].

Classification

A) Primary Thrombocytosis (Essential thrombocytosis) - This is due to a failure to regulate the production of platelets (autonomous production) and is a feature of a number of myeloproliferative disorders. About a third of patients are asymptomatic at the time of diagnosis[13].

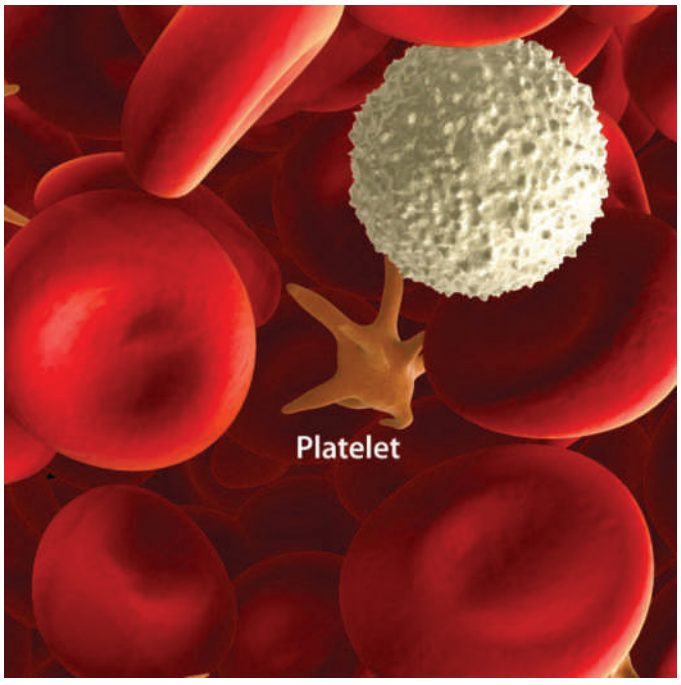

Figure 4(a): Low Platelet Count

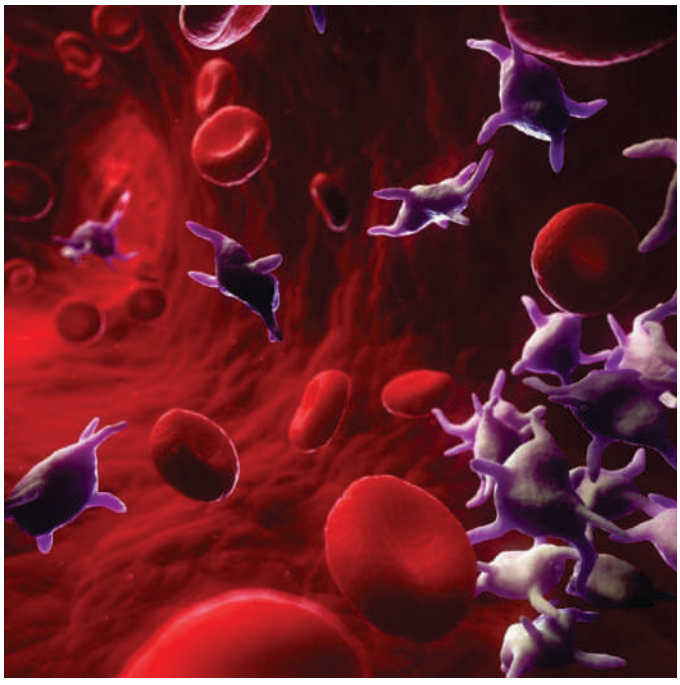

Figure 4(b): High Platelet Count

B) Secondary Thrombocytosis (Reactive thrombocytosis) - This can be secondary to a number of conditions. It is an exaggerated physiologic response to a primary problem, such as an infection. The trigger factor (e.g. infection) results in the release of cytokines which mediate an increase in platelet production. It is often a transient phenomenon which disappears when the underlying cause is resolved[14].

C) Non-specific Thrombocytosis - A recent "expert panel" has recommended that a platelet count of 400-450,000 needs no further evaluation.[15] Any platelet count > 450,000 does need evaluation. If there is no evidence of a "reactive" thrombocytosis, then Janus Kinase 2 mutations (JAK-2) testing should be done. A bone marrow biopsy should also be done, which would include testing for the Ph+ chromosome. Commonly, if these tests are negative, the individual platelet count is between 450,000/µl and 600,000/µl, and no evidence of reactive process then the individual is labeled "non-specific thrombocytosis."

Causes of Thrombocytosis[12]

I. Physiological: Exercise, Parturition, and Epinephrine

II. Pathological:

A) Primary Thrombocytosis

1) Myeloproliferative disorders.
   - Polycythemia vera
   - Chronic myeloid leukemia (CML)
   - Chronic idiopathic myelofibrosis
   - Essential thrombocytosis

2) Myelodysplastic disorders

3) Hereditary thrombocytosis

B) Secondary Thrombocytosis

1) Infection
   - Meningitis,
   - Infections of the upper and lower respiratory tract,
   - Urinary tract infections,
   - Gastroenteritis,
   - Septic arthritis,
   - Osteomyelitis and Generalised sepsis.

2) Chronic inflammations and vasculitis
   - Rheumatoid arthritis,
   - Kawasaki syndrome,
   - Henoch-Schonlein purpura,
   - Inflammatory bowel disease.

3) Tissue damage
   - Postsurgical,
   - Burns,
   - Trauma,
   - Fracture.

4) Rebound thrombocytosis
   - Iron deficiency anemia,
   - Bleeding,
   - Cancer chemotherapy,
   - Recovery phase of idiopathic thrombocytopenic purpura (ITP)

5) Postsplenectomy

6) Haemolytic anemia

7) Renal disorders (for example nephrotic syndrome, nephritis)

8) Malignancy (especially soft tissue sarcoma, osteosarcoma)

9) Low birth weight/ preterm infants.

Pathophysiology of Reactive Thrombocytosis[12]

Reactive thrombocytosis is usually mediated by increased release of numerous cytokines in response to infections, inflammation, vasculitis, tissue trauma, and other factors. Thrombopoietin (TPO), the primary cytokine for platelet production and maturation, and interleukin (IL)-6 levels are usually initially elevated in response to the primary events mentioned earlier; they stimulate an increase in platelet production.

It may be due to the overproduction of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-11, that occurs in chronic inflammatory, infective, and malignant states. The presence of elevated IL-1, IL-6, C-reactive protein (CRP), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in individuals with these conditions suggests that these cytokines may be involved in secondary thrombocytosis (reactive thrombocytosis).

However, serum or plasma levels of these cytokines do not seem to be correlated with degree of thrombocytosis. Other cytokines may participate in the stimulation of platelet production. They include IL-3, IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin. These cytokines are directly or indirectly released during the primary events. When the original stimulation stops, the platelet count then returns to the reference range.

In severe infections, such as bacterial meningitis, one of the causes may be a rebound phenomenon after initial thrombocytopenia due to rapid consumption of platelets. This most commonly occurs in neonates and infants, indicating the labile nature of platelet count control in these subjects.

The most common infection associated with thrombocytosis is

pneumonia. In some instances, such as chronic haemolytic anemia, the stimulus (hypoxia) to produce cytokines persists, causing long-term elevation of platelet counts. Although thrombocytosis in association with iron-deficiency anemia is well documented, the mechanism remains unclear. Although elevated erythropoietin levels are observed in patients with thrombocytosis who have iron-deficiency anemia, a recent study showed that these elevated levels had no correlation with platelet count. Levels of other cytokines potentially responsible for thrombocytosis, such as IL-6 and TPO, were not elevated.

The spleen is the major organ for the destruction of platelets; therefore, after splenectomy, a sharp rise in the platelet count is routinely observed, although the count subsequently slowly decreases to the reference range. Similarly, functional asplenia that may occur after splenic artery embolisation results in thrombocytosis.

Laboratory Findings in Reactive Thrombocytosis

There was no specific laboratory finding in patients with reactive thrombocytosis, and the diagnosis ultimately depends on diagnosing the underlying problem. Serum IL-6 concentrations measured by activity assay of ELISA are increased in majority of patients believed to have reactive thrombocytosis and in of the patient with clonal megakaryopoesis, but these tests are not clinically available. Hollen found increased serum concentrations in 80% to 100% of his patients with malignancy, inflammation or recent surgery. Only 50% of the anaemic patients had increased concentration of IL-6 and only one of five patients were in this group[12].

Elevated fibrinogen levels are found in patients of reactive thrombocytosis, presumably as a part of acute-phase reaction, and may be helpful in differentiating primary from secondary thrombocytosis[16].

Serum obtained from patient with thrombocytosis may contain elevated concentration of acid phosphates or potassium. In blood samples containing increased number of platelets, the PaO_2 may be significantly reduced due to consumption of oxygen by the platelet, particularly if the blood sample is stored at the room temperature[16].

In one study done by Perez Encinas et al[36] in 1995, they found the most potent stimulator for the hepatic synthesis of C-reactive protein is interleukin-6. Also, interlukin-6 is endowed with thrombopoietic activity and its level increases in most of the reactive thrombocytosis where as they remain normal in primary thrombocytosis. They had concluded that Quantitation of C-reactive protein could thus prove useful in differentiating between primary and reactive thrombocytosis[17].

Differential Diagnosis of Thrombocytosis

Clinical and laboratory features that distinguish between primary (ET) and secondary thrombocytosis (RT)[12].

Features	ET	RT
1. Thrombosis and haemorrhage	+	-
2. Splenomegaly	+	-
3. Increased acute-phase reactants (IL-6, CRP and plasma fibrinogen)	+	-
4. Bone marrow reticulin fibrosis	+	-
5. Bone marrow megakaryopoesis clusters	+	-
6. Clonal haematopoiesis	+	-
7. Spontaneous colony formation	+	-
8. Abnormal cytogenetic	+	-

Prognosis

Most patients with reactive thrombocytosis do not have significant problems caused by thrombocytosis, and the prognosis of the basic disease is not usually significantly affected.

Thrombocytosis in Childhood[18]

Thrombocytosis is a frequent finding in hospitalized and ambulatory children due to the widespread use of automated blood cell counters. Reactive thrombocytosis is very common and is due to a variety of conditions

Causes of Secondary or Reactive Thrombocytosis in Children[18]

1. Infections (e.g., of the respiratory tract, gastrointestinal tract, urinary tract infections central nervous system, skeleton and others)
2. Iron deficiency anemia, haemolytic anemia
3. Bleeding
4. Connective tissue diseases (juvenile rheumatoid arthritis, small and large vessel vasculitis including Wegener's granulomatosis, polyarteritis nodosa and others)
5. Kawasaki's disease
6. Inflammatory bowel diseases
7. Langerhan's cell histiocytosis
8. Malignancies (mostly solid tumours, such as hepatoblastoma, hepatocellular carcinoma, neuroblastoma, and rarely acute lymphoblastic leukaemia)
9. Drugs (adrenaline, corticosteroids, vinca alkaloids, iron, miconazole, antibiotics, haloperidol, narcotics, and non-narcotic psycho pharmaceutical agents)
10. Trauma, burns, tissue injury
11. Intense exercise
12. Splenectomy (surgical or functional e.g., sickle cell anemia)

It seems to affect up to 15% of hospitalized children[19-25]. It is more common in neonates, particularly premature ones, and infants up to 2 years of age and less common in older children. In most children with reactive thrombocytosis, platelet counts

are moderately elevated up to 700,000/µl. Moderate thrombocytosis (platelets between 700,000 and 899,000/ µl) occur in 6-8% of children with reactive thrombocytosis, while platelets >1,000,000/µl occur in less than 2-3% of children with reactive thrombocytosis[22].

Presently, **infections** of the respiratory tract account for 60-80% cases of secondary thrombocytosis in children[20,22-27], followed by infections of the urinary[28] and gastrointestinal tracts, and of the bones[22-24,27,29].

From the **non-infectious** causes of secondary thrombocytosis, iron deficiency anemia is a common one, since it is the single most common nutritional deficiency worldwide[30,31]. The fact that thrombocytosis is more frequent in children up to 2 years of age is partly due to the higher incidence of iron deficiency in this age group.

In patients with **systemic-onset JRA,** serum IL-6 levels correlate with platelet counts and with the extent and severity of joint involvement[32]. Regarding **Kawasaki's disease (KD),** thrombocytosis typically occurs in the second week of the illness, and it is therefore not helpful in making a timely diagnosis. Moreover, the absence of thrombocytosis during convalescence does not exclude the disease. TPO in conjunction with IL-6 contributes to the thrombocytosis of patients with KD. TPO serum levels are also increased in patients with inflammatory bowel diseases, irrespective of disease activity, platelet counts and clinical characteristics of the patients[33].

The association between **liver tumours** and thrombocytosis is likely due to the increased production of hepatic TPO in these patients. Reactive thrombocytosis has also been described in children with other small, blue round cell tumours of childhood, such as **neuroblastoma**[34].

Reactive thrombocytosis can also be related to treatment with several drugs. **Adrenaline and corticosteroids** are known to cause transient thrombocytosis, as a result of release of stored platelets from the spleen into the blood circulation[35]. Various antibiotics such as **carbapenems and cephalosporins** are also claimed to cause thrombocytosis in children[36-43]. In the first week, when platelet counts are normal, circulating TPO concentrations rise and then gradually decrease. When platelet counts peak during convalescence, TPO concentrations are back to normal. Hence, the development of thrombocytosis during the recovery phase after appropriate antibiotic therapy for an infection is consistent with the bone marrow response to TPO and not the result of the antibiotic[43,44].

Miconazole, ciprofloxacin and tazobactam/ piperacillin caused thrombocytosis in a single patient18 since the platelet count started to increase immediately after initiation and dropped immediately after discontinuation of the drug[39].

Neonatal reactive thrombocytosis has been described from **maternal narcotic drug abuse,** but may also occur in infants born to mothers treated during pregnancy with non-narcotic psycho pharmaceutical agents[45,46]. Finally, reactive thrombocytosis may be due to multiple, simultaneous, causative factors. In one paediatric series, 9% of cases of secondary thrombocytosis were multi-factorial[47].

Reasons for reactive thrombocytosis in different clinical conditions:

1) Inflammations and Infections:

Thrombopoietin (TPO), the primary cytokine for platelet production and maturation, and interleukin (IL)-6 levels usually stimulate an increase in platelet production. Thus, it may be due to the overproduction of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-11, that occurs in chronic inflammatory, infective, and malignant states.

2) Iron Deficiency Anemia:

Reactive thrombocytosis is usually of mild to moderate degree. Extreme thrombocytosis is not so common but in some patients it can occur. Thrombopoietic growth factors including interlukin-6(IL-6), tumour necrosis factor-alpha, and thrombopoietin have been implicated as the cause of reactive thrombocytosis. Several clinical and the laboratory observation support the possible pathogenic role of elevated IL-6 in reactive thrombocytosis. An alteration of the bone marrow megakaryocyte count in iron deficiency anemia is not mentioned except for the two reports. In these reports authors mentioned that the bone marrow megakaryocyte count was increased and the plausible explanation for the thrombocytosis must be increased production of the platelet. The mechanism causing reactive thrombocytosis in iron deficiency anemia is unknown.

3) Tissue damage from trauma or surgery (postoperative):

The platelet count increases when a relatively large amount of body tissue is damaged either intentionally following surgery or after an accident. This is because of body natural defence mechanism to ensure adequate clot formation and prevent fatal bleeding.

4) Blood loss:

In event of an injury, the response of the bone marrow to blood loss is to produce more red blood cells and more platelets.

5) Post-splenectomy:

The splenectomised patients are expected to have high postoperative platelet counts because of reduced platelet storage in the spleen. The increase may remain for a long time, but usually it settles back into the normal range.

6) Haemolytic anemia:

Haemolytic anemia is another frequent cause of thrombocytosis. Sickle cell anemia is a congenital haemolytic anemia associated with thrombocytosis due to increased bone marrow platelet production, but also due to functional asplenia from the repetitive splenic autoinfarcts. Patients with sickle cell anemia and thrombocytosis are at

increased risk for vaso-occlusive complications, such as brain infarcts, painful crises, while they have highly impaired full scale IQ[48,49].

7) Malignancy:

Malignancy causes high platelet count either by causing damage to tissues, causing blood loss (for example from the bowel) or by erroneously producing a response from the immune system that stimulates the bone marrow to produce platelets.

8) Tuberculosis:

The pathogenesis of reactive thrombocytosis in tuberculosis is not clear. It has variously been attributed to increase thrombopoietin[50] or production of platelets in pulmonary vasculature by fragmenting proplatelets[51].

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Short Review

A Short Review on Potential Extra-skeletal Benefits of Vitamin D with Special Reference to Type-2 Diabetes mellitus

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ABSTRACT

Vitamin D, the "sunshine vitamin" mainly benefits bones and muscles. Over the past few decades, it has generated lot of interest in scientific community regarding its extra skeletal health benefits. These benefits range from neurodegenerative diseases to metabolic conditions, cardiovascular disease, lung infection and cancer. The present short review will highlight its extra skeletal beneficial health effects in particular the present thinking on vitamin D and diabetes mellitus.

KEYWORDS: Sunshine vitamin, Eldecalcitol, Cholcalciferol, Pre-diabetes, Insulin Resistance

INTRODUCTION

Vitamin D has been incriminated as the main factor promoting growth and fitness of bones as well as cognitive health. Over the past few decades, interest has been generated for its extra skeletal health benefit. There are many clinical situations which have been linked to Vitamin D deficiency states. Interestingly but really alarming, Vitamin D deficiency has become a common biochemical finding. It is difficult to trace the exact cause of Vitamin D deficiency, but the two important mechanisms are the possibilities. Firstly, the vitamin is not found in a lot of commonly eaten food and secondly, the primary source, the sun, its exposure may be limited depending upon the living conditions and social upbringing.

Extra-skeletal Health Benefits of Vitamin D

Vitamin D and Respiratory Infections

The role of vitamin D has been linked to respiratory illness including COVID-19. Preliminary research data found that Vitamin D supplementation may be beneficial in preventing the common respiratory illness. In a systemic review and meta-analysis, it was found that Vitamin D supplementation protected against the respiratory tract infection without side effects. The patients, in whom the Vitamin D levels were very low, benefited most[1].

As far as the connection between Vitamin D levels and COVID-19 is concerned, it is still not authenticated. However, in an unpublished study by researchers at North Western University in Chicago, observed that countries with high prevalence of Vitamin D deficiency had higher rates of COVID-19 mortality rate. Vitamin D has been known to play a role in immune system and there are Vitamin D receptors on immuno competent cells. Vitamin D deficiency therefore, may increase the body`s susceptibility to infection and its supplementation is therefore beneficial[1].

Vitamin D and Psychiatric illnesses

Vitamin D is also nicknamed as "sunshine vitamin" and conditions like seasonal affective disorder and depression are linked with its deficiency.

In a study (Sunshine Study) conducted on women with type 2 diabetes who had significant depressive symptoms and were administered 50,000iu of Vitamin D weekly for six months. The result obtained was, that there was a significant ($p<0.001$) decrease in depression and anxiety along with improvement in mental health[2].

A strong association was found between vitamin deficiency and schizophrenia in a systematic review and meta-analysis from 19 observational studies[3].

Vitamin D and risk of dementia including Alzheimer disease was assessed in more than 1600 elderly people without dementia at the start of the study. Comparing the Vitamin D levels in those who had normal values and those with low levels; it was observed that people with low levels of vitamin D had a 53 percent more risk of developing all-cause dementia. On the other hand, those were severely deficient had a 125 percent increased risk of developing dementia. People with lower levels of Vitamin D were 70 percent more chance to develop Alzheimer`s disease specifically, while severely deficit individuals had more than 120 percent chance to develop this neurodegenerative disorder of elderly[4].

Prostate Cancer Risk and Vitamin D Levels

In a meta-analysis of 21 relevant publications including 11,941 cases and 13,870 controls, it was revealed that a significant 17 percent increased risk of prostate cancer for the study subjects with higher levels of Vitamin D[5]. On the contrary, previous study reported earlier, found a link between low levels of Vitamin D and aggressive prostate cancer in African American and European men.

Vitamin D and Breast Cancer

Besides prostate cancer, a link has also been seen with Vitamin D deficiency and breast cancer. A review published in 2018 found that most of the studies support that there is an inverse association between the level of Vitamin D and the risk of breast cancer[6,7].

Erectile Dysfunction and Vitamin D Levels

A small study conducted on 143 patients with varying severity of erectile dysfunction (ED) to assess their Vitamin D levels. They found that the men with severe ED had significantly lower Vitamin D levels than the men with mild ED. Furthermore, it was interesting that this combination of ED with low level of Vitamin D was more frequent in patients with arteriogenic etiology, suggesting that low levels of Vitamin D may increase ED by promoting endothelial dysfunctions[8].

Vitamin D Deficiency and Cardiovascular Diseases

Literature reviewed points towards the relation between Vitamin D and heart problems. It may be a potential risk factor for health problems related to heart disease including hypertension, atherosclerosis, diabetes and stroke. However, it still not established whether Vitamin D supplementation will reduce the cardiac risk.

A recent study, conducted on Vitamin D supplementation and development of cardiovascular events, indicated that Vitamin D supplementation might reduce the incidence of major cardiovascular events, but absolute risk difference is small. However, it can also not be concluded that Vitamin D administration does not alter the risk of cardiovascular diseases[9].

Vitamin D and Diabetes

The exponential increase of T2DM is a great cause for concern and if left untreated, T2DM can lead to a multitude of chronic microvascular and macrovascular conditions such as retinopathy, nephropathy, neuropathy and cardiovascular disease (CVD)[10]. The enormity of the T2DM epidemic and its sequelae emphasize the importance of finding ways to prevent and/or ameliorate the deleterious effects of this disease. In addition to genetics which predisposes individuals to developing T2DM, there are also many environmental factors which contribute greatly to its development[11]. A plausible explanation of pathophysiology of T2DM is a requisite to understand the relationship between Vitamin D status and T2DM before reviewing the evidences for their association.

PATHOGENESIS OF TYPE 2 DIABETES:

In a normoglycemic individual, in response to a rise in blood glucose, the β-cells of the islets of Langerhans, found within the pancreas, will synthesize and secrete insulin into the blood[12]. A malfunctioning of the feedback loops between insulin action and insulin secretion results in abnormally high glucose levels in blood[13]. T2DM is a progressive chronic disease; it begins with insulin resistance, which leads to increases in hepatic glucose production and ends with β -cell failure[14,15].

In the case of β-cell dysfunction, insulin secretion is reduced, limiting the body's capacity to maintain physiological glucose levels. On the other hand, IR contributes to increased glucose production in the liver and decreased glucose uptake both in the muscle, liver and adipose tissue[16].

T2DM pathophysiology involves at least seven organs and tissues, including the pancreas, liver, skeletal muscle, adipose tissue, brain, gastrointestinal tract, and kidney (Figure 1). Reduced sensitivity to insulin (i.e., impaired insulin-mediated glucose disposal or insulin resistance) in liver, muscle, and adipose tissue, and a progressive decline in pancreatic β-cell function leading to impaired insulin secretion, eventually result in hyperglycemia, the hallmark feature of T2DM[17].

VITAMIN D AND T2DM:

Synthesis of 1, 25-Hydroxyvitamin D:

When the skin is exposed to solar ultraviolet B radiation (wavelength, 290 to 315 nm), 7-dehydrocholesterol is converted to pre-vitamin D3, which is rapidly converted to Vitamin D3 (cholecalciferol).Vitamin D from the skin and diet is then transported in the blood by circulating vitamin D-binding protein (DBP, a specific binding protein for Vitamin D and its metabolites in serum).

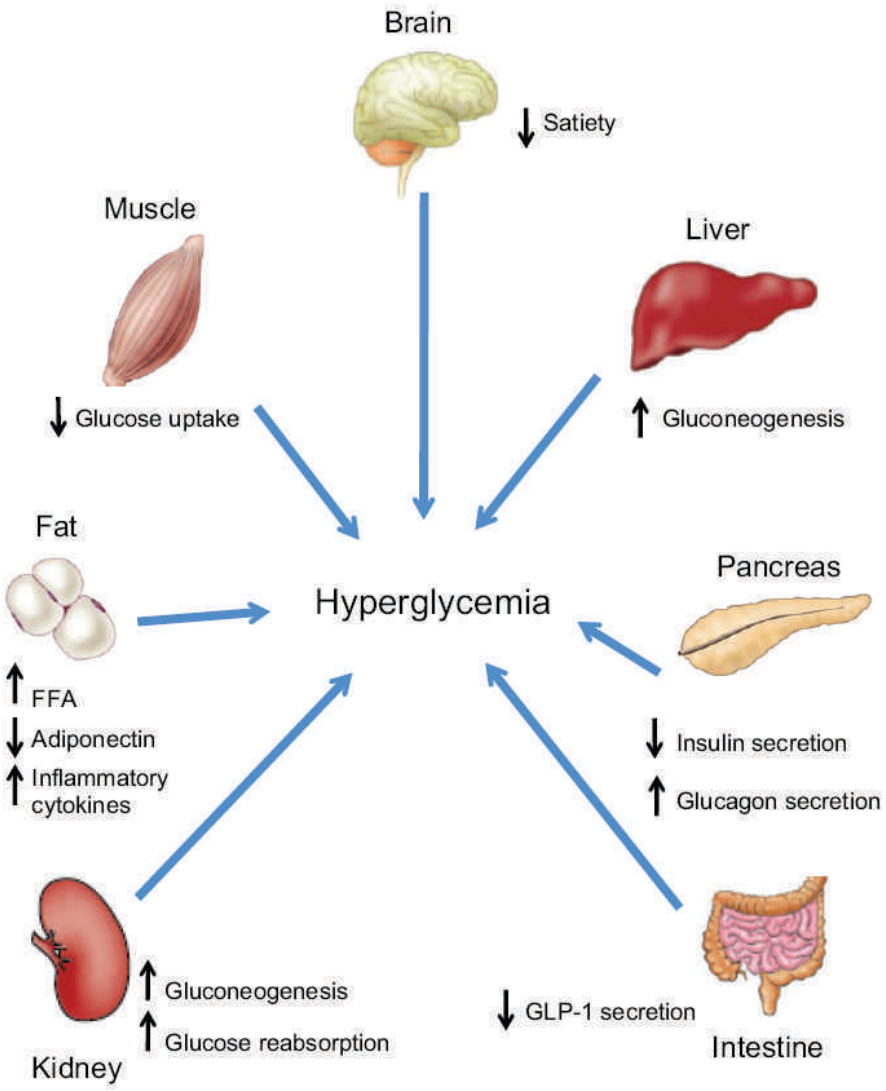

Figure 1: Multi-organ and tissue pathophysiology of type 2 diabetes[17]

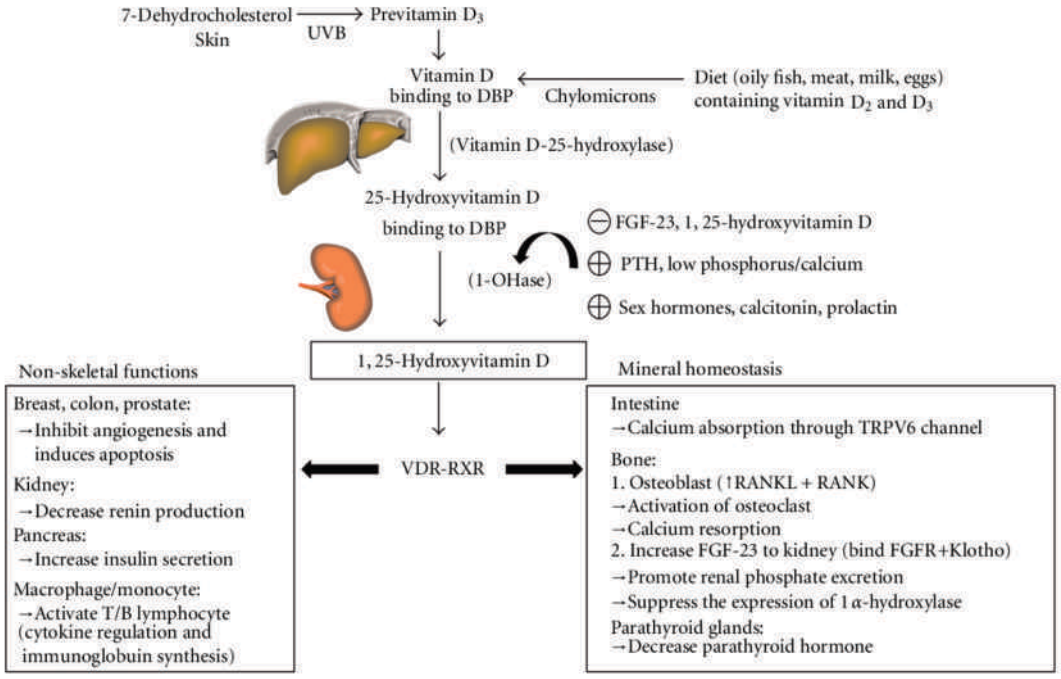

Figure 2: Synthesis and Metabolism of vitamin D in the regulation of mineral homeostasis and Non-skeletal functions.[18]

Link between Vitamin D Deficiency and Insulin Resistance:

Vitamin D has been proposed to play an important role and to be a risk factor in the development of insulin resistance and the pathogenesis of type 2 DM by affecting either insulin sensitivity or β-cell function, or both[19].

In keeping with the notion that T2DM cannot manifest without β-cell failure, it is important to examine the role of Vitamin D metabolites (i.e., 1, 25(OH) 2D3) in pancreatic β-cell function. Vitamin D is reported to be essential for insulin secretion from pancreatic β–cells[20] in both in vitro and in vivo studies[21,22,23]. The mechanisms by which Vitamin D acts on insulin secretion are thought to be both direct and indirect; in particular, the direct effect of vitamin D on insulin synthesis and secretion is suggested by the demonstrated binding of the active form 1, 25(OH) D to the vitamin D receptor on β-cells, by the identification of vitamin D response elements in the human insulin gene promoter[24], and by the transcriptional activation of the human insulin gene caused by 1, 25(OH) D25. Instead, the indirect effects of Vitamin D on β-cell secretory function seem to be mediated by alterations in calcium flux through the β-cell membrane, as suggested by a study conducted by Beaulieu *et al.*[26].

Another plausible explanation given is based on low-grade inflammation characterized by increase in circulating cytokines, which is one of the hallmarks of T2DM. High amounts of circulating inflammatory cytokines, such as TNF α and IL-6, contribute significantly to insulin resistance in muscle and adipose tissue[27]. To help establish a protective role for vitamin D and its respective metabolites against T2DM, **Riachy et al.** examined the effects of 1,25(OH)2D3 on human islets in the presence of cytokines and found that islets incubated with cytokines and 1,25(OH)2D3 were protected against apoptosis compared to those incubated with cytokines alone[28]. Moreover, the identification of the VDRE in the insulin receptor gene promoter has also helped establish a role for 1, 25(OH) 2D3 in increasing insulin sensitivity by increasing insulin receptor gene expression[24]. Furthermore, Vitamin D3 supplementation has been shown to reduce inflammatory cytokines such as IL-6 and TNF-a, which play a significant role in inducing insulin resistance[29].

Following chart summarize the role of Vitamin D deficiency in Insulin Resistance and hence, Diabetes as per the evidences available from literature:

In order to assess the correlation between Vitamin D levels and diabetes mellitus, many prospective case control and cross-sectional studies have been conducted throughout India as well as the globe. In India, results have been reported from Kolkata, Eastern India, Tirupati from south and Rajasthan from the west. Other studies have been reported from Kenya, Saudi Arabia, Korea, Brazil and Riyadh. Many reviews and meta-analysis of randomized controlled trials have also been published with different population and subsets of patients.

Role of Vitamin D Deficiency in Insulin Resistance	Study Reference
Inherited gene polymorphisms • Including DBP, VDR, and CYP1alpha gene polymorphisms • Disturbance of Vitamin D transport, action, and production	18,30,31
Immuno-regulatory function • Activating innate and adaptive immunity • Enhancing dendritic cell maturation and macrophage differentiation, and cytokine release • Enhancing T-cell proliferation Releases of IL-12, IL-2, INF-γ, and TNFα (destruction of the β-cell)	18,32-34
Inflammation • Upregulation of NF-κB and inducing TNFα proinflammatory actions • Downregulates IκB-α by decreasing mRNA stability and increasing IκB-α phosphorylation. • Enhancing the expression of TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines	24,27-29,35
Other molecular actions of vitamin D to alter glucose homeostasis • Low calcium status: hypocalcemia can lower glucose-stimulated insulin secretion in β-cell • PTH level: elevating PTH reduces glucose uptake by liver, muscle and adipose cell • Obesity: Vitamin D deficiency can increase adiposity, and increasing sequestration of Vitamin D in adipose tissue TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines	18,36,37

REVIEW OF STUDIES

A prospective case control study found out the Vitamin D status in newly detected T2D patients. One hundred and two, newly detected T2D patients and similar number of age, body mass index (BMI), and gender matched healthy controls without diabetes were studied. Overall 25HD, was lower (mean ± SD, 18.81 ± 15.18 ng/ml) in patients with T2D as compared to healthy controls (28.46 ± 18.89 ng/ml). Severe VDD (25HD of < 5 ng/ml) was seen in 16.2% of patients with diabetes and 2.5% of control subjects. Conclusion was drawn that the mean serum 25HD was significantly lower in people with diabetes compared with controls[38].

To determine the prevalence of Vitamin D deficiency in Asian Indians with Type 2 diabetes mellitus (T2DM) living in north India a study was conducted on a total of 92 patients with T2DM and were compared with nondiabetic patients (n = 92) matched for age, gender, BMI, waist circumference and total body fat. The average concentration of serum 25(OH) D3 was significantly lower for T2DM patients as compared with non-diabetic patients. Severe vitamin D deficiency was significantly more prevalent among T2DM patients (57.6%) than the non-diabetic patients (33.3%). The average concentration of serum 25(OH) was significantly lower for diabetic males than diabetic females (9.07 ± 6.7 vs. 12.6 ± 7.6, p = 0.02). Conclusion was made that the prevalence of severe Vitamin D deficiency among Asian Indians living with T2DM in a metropolitan city of north India was greater than those without T2DM and this difference was statistically significant[39].

The occurrence of Vitamin-D insufficiency/ deficiency among Pre-diabetics and the relationship between Vitamin-D status and insulin resistance was also addressed in a study carried out on 157 pre-diabetics along with 42 diabetics and 28 controls attending department of Endocrinology and Metabolism, Institute of Postgraduate Medical Education & Research, (IPGMER) and SSKM hospital, Kolkata, India.It was estimated that out of 157 subjects Vitamin-D deficiency/ insufficiency was 73.25% (n=115), 66.6% (n=28) and 78.57 % (n=22) in individuals with pre-diabetes, diabetes and controls respectively. A statistically significant inverse correlation was observed between Vitamin D and insulin resistance (HOMA2-IR; r=-0.33, P=0.008); and a positive correlation with measures of insulin sensitivity (QUICKI, 1/fasting insulin). Conclusion was drawn that Vitamin-D deficiency/insufficiency may play role in the development or worsening of insulin resistance in pre-diabetic individuals[40].

In a cross-sectional study conducted in a Tertiary Care Hospital of Eastern India, the prevalence of Vitamin D deficiency in new onset type 2 diabetes mellitus as well as the association between 25 hydroxy vitamin D with insulin resistance and insulin secretion was explored. The study was carried out for a duration of 18 months over 120 newly diagnosed cases of type 2 diabetes which were compared with 120 non-diabetic healthy controls. Results showed that there was significantly lower vitamin D level ($p< 0.001$) in cases (mean =24.91± 14.58 ng/ml) as compared to controls (mean=41 ± 28.33 ng/ml). 30% subjects (n=36) and 29.16% (n=35) were having insufficient Vitamin D levels among cases and controls respectively. Similarly, 30% (n=36) and 19.16% (n=23) were deficient among cases and controls respectively. As per the revealed results conclusion was drawn that 25(OH) D had significant negative association with insulin resistance[41].

Prevalence of hypovitaminosis D among type 2 diabetic patients at Kenyatta National Hospital in Nairobi, Kenya was determined through a cross-sectional study. A total of 151type 2 diabetic patients on follow-up were recruited. Results reported that the mean Vitamin D level was 31.40 ng/ml (±23.22). Vitamin D deficiency was found in 58 study participants (38.4%). The study brought out that population on a long-term follow-up for diabetes, there was high prevalence of vitamin D deficiency. This forms a basis for further management of patients with poor glycemic control[42].

A cross-sectional study investigated the prevalence Vitamin D deficiency in male patients with T2DM. 1145 patients with T2DM attending the Diabetes centre at King Fahad Armed Forces Hospital, Saudi Arabia between January 2018 and December 2018. The prevalence of different Vitamin D status were; 55.6% deficient, 27.3% insufficient and 17.0% sufficient. Vitamin D deficient patients have statistically significant higher HbA1c than patients with vitamin insufficiency or sufficiency (8.3 ± 2.0 vs. 7.7 ± 1.7 vs. 7.4 ± 1.7 respectively, $p<0.0001$). Moreover, Vitamin D deficient patients have statistically significant lower 25(OH) D than patients with vitamin insufficiency or sufficiency (34.3 ± 8.9 vs. 60.6 ± 7.2 vs. 100.3 ± 23.0 respectively, $p<0.0001$). The mean 25(OH) D was upward as age advanced with highest frequency of VDD was found in the sixth decades. Conclusion revealed that the prevalence of VDD in male patients with T2DM was high[43].

A cohort study explored the association between 25-hydroxy vitamin D and type 2 diabetes (T2D) risk. 1080 nondiabetic Korean subjects based on the presence of one or more risk factors for T2D, including obesity, hypertension, dyslipidemia, and/ or family history of T2D were recruited for the study and followed up for 5 years. Anthropometric and biochemical indicators, HOMA2-IR, and the insulinogenic index (IGI) were measured. Results revealed that 0.5% had a serum 25(OH) D deficiency, 51.6% had an insufficiency and 38.0% had a sufficiency. Out of 1080 participants, 97 (9.0%) developed T2D over 32.3 6 15.6 months of observation. The incidence rates of T2D (Hb A1c $\geqslant$6.5%) came out to be 15.9%, 10.2%, and 5.4% in the 25(OH) D-deficient, insufficient, and sufficient groups, respectively ($P < 0.01$). It was concluded that independently of known risk factors, Vitamin D metabolism play a role in pathogenesis of T2D[44].

Blood levels of Vitamin D3 and its association with type 2 DM in rural ethnic population was assessed in a cross- sectional study undertaken from February 2018 to January 2019 at Multidisciplinary Research Unit of Agartala Government Medical College. A total of 208 ethnic subjects were recruited in this study using multistage sampling technique. 65% prevalence of Vitamin D3 insufficiency was observed as per the reported results. It was revealed that out of 208, 136 subjects had blood Vitamin D3 insufficiency while 72 subjects were with sufficient amount of Vitamin D3 level. The findings of this study also suggested a much higher prevalence of Vitamin D3 insufficiency in the age range of 51–61 years[45].

A prospective study was carried out in D. Y. Patil University, School of Medicine for a duration of 1 year to assess the correlation of Vitamin D deficiency with T2D and metabolic risk factors in Indian population. A total of 144 subjects were recruited for the study, out of which 74 were diabetic and 70 were non-diabetic controls. Analysis of the data revealed that 13.51% of the diabetics to be Vitamin D deficient as compared to 28.57% deficient among the non-diabetics. This study found out an inverse relation between Vitamin D and serum cholesterol ($p=0.01$) and it was also statistically significant for Vitamin D and low-density lipoprotein ($p=0.01$)[46].

In another study conducted in 2017, the association between serum Vitamin D levels and glycemic control markers in type 2 DM patients was analysed. 80 diagnosed subjects of Type 2 DM reporting to Endocrinology and Metabolism outpatient department of Sri Venkateswara Institute of Medical Sciences, Tirupati were included in the study. Subjects were divided into two groups; n=38 (with Vitamin D >20 ng/mL - Vitamin D non-deficient) and n = 42 subjects with Vitamin D $\leqslant$ 20 ng/ mL (Vitamin D deficient). Results revealed that there was no significant association between Vitamin D and markers of glycemic control- FBS, PPBS, HbA1c and Insulin resistance[47].

The relationship between Vitamin D levels and ages of type 2 diabetes individuals was assessed in a descriptive-analytical study conducted on 101 type 2 diabetes patients. The mean age of the subjects was 61.25 ± 11.75 years. Out of 101 diabetic patients, 72 individuals suffered Vitamin D deficiency which is 71.3%. Findings of the study suggested that serum Vitamin D levels of type 2 diabetic subjects were significantly correlated with their ages ($r = 0.282$, $P = 0.004$)[48].

Another study determined the vitamin D status among type 2 diabetics and examined the association of Vitamin D status with level of glycemic control. Subjects were divided into 3 groups- group I consisting of 48 healthy controls, group II having 46 patients with DM history of more than five years and HbA1c levels < 7% and Group III comprising of 56 patients with DM history of more than five years and HbA1c levels > 7%. Results of the study showed that diabetic patients had lower Vitamin D levels in comparison to healthy individuals and the value further decreases in patients with poor glycemic control (HbA1c >7%). It was also concluded that there was

significant negative correlation between HbA1c and Vitamin D levels (r= -0.94 and -0.97 respectively)[49].

Prevalence of Vitamin D deficiency and its correlation with diabetes among menopausal women was also evaluated in a cross sectional one year analysis. A total of 312 Post-menopausal women were recruited in this study. Fasting blood glucose levels were used to analyse any Correlation between raised blood sugar levels and Vitamin D deficiency among postmenopausal women (PMW). Although results have shown high Vitamin D deficiency (53.35%) among the study population but it failed to show any statistical significant association between Vitamin D deficiency and existence of diabetes. Conclusion was made that statistical correlation between Vitamin D deficiency and existence of diabetes was not significant because of the small sample size[50].

The effect of Vitamin D supplementation on glycemic control and insulin resistance in Type 2 Diabetes Mellitus was explored in a Pre-post Intervention Trial. Fasting and postprandial blood samples were collected from the 300 known cases of Type 2 Diabetes mellitus and controls, which were further divided into 2 groups- Group I (subjects with normal Vitamin D level >20ng/ ml), no Vitamin D supplementation was given, whereas Group II (with decreased Vitamin D level <20 ng/ml), oral supplementation of Vitamin D, 60,000IU/week for 4 weeks was given. Results showed that prevalence of Vitamin D deficiency (< 20 ng/mL) in type II diabetes individuals was 30%. It was revealed that after supplementation to the Vitamin D deficient Diabetic group there was a significant decrease in Fasting plasma glucose (p-value 0.0028). Also, a statistically significant decrease was observed in Fasting serum insulin levels (p <0.0031) and insulin resistance (p=<0.0001) after 4 weeks of Vitamin D supplementation. The Conclusion was drawn that Vitamin D supplementation in Diabetics could be beneficial in management of Type 2 DM[51].

Correlation between Vitamin D level and glycemic control in type 2 diabetics was investigated in a study conducted on 50 type-2 diabetes patients attending Medicine OPD and Geriatric OPD in PBM Hospital Bikaner Rajasthan. Result of this study revealed an inverse between Vitamin D level and HBA1c which meant Vitamin D status is inversely related to glycemic control. The conclusion was made that Vitamin D deficiency is prevalent in type 2 diabetes mellitus patients. Hence, supplementation of Vitamin D can improve their glycemic control which can further reduce the complication of diabetes[52].

The status of Vitamin D among type 2 diabetes mellitus patients was investigated in a systematic review including 12 Saudi studies. There were nine cross-sectional studies, two randomized case-control studies and one study whose design was not mentioned. In 10 studies14,373 T2DM patients participated and in the remaining studies there were 272 T2DM patients and 273 controls. Results showed that the prevalence of Vitamin D deficiency varied in a range of37.6% to 80% among the included studies. Four studies found that HbA1c was higher among T2DM patients with Vitamin D deficiency than patients without deficiency of the vitamin. On the contrary three studies found a negative correlation between HbA1c and Vitamin D deficiency, where HbA1c was higher among T2DM patients without Vitamin D deficiency. It was concluded that the prevalence of Vitamin D deficiency was high among T2DM patients especially among older patients[53].

Predictors of hypovitaminosis D in patients with type 2 diabetes mellitus patients were identified in a cross-sectional study on 108 patients recruited from Endocrinology outpatient clinic, Brazil. Results of the study revealed that the overall prevalence of hypovitaminosis D was 62% (39.8% insufficient and 22.2% deficient). In this study p = 0.02), dyslipidemia (OR 6.50, p < 0.01) and obesity (OR 2.55, p = 0.07) emerged as independent predictors of Vitamin D deficiency. HbA1c ($r = -0.22$, $p = 0.03$) showed significant inverse linear correlations with vitamin D levels. Based on these results conclusion was made that future studies are needed to evaluate whether vitamin D replacement would help reducing cardiovascular outcomes[54].

The impact of Vitamin D on glycemic control in patients with type 2 diabetes mellitus was analysed in a study conducted on 128 diabetic patients. Based on HBA1c values patients were divided into two groups: good glycemic control (HbA1c⩽7%) and poor glycemic control (HbA1c>7%). In this study Vitamin D deficiency rate was found to be 98.3%. Although there were high level of Vitamin D deficiency, results of this study indicated that Vitamin D was not significantly associated with glycemic control in type 2 diabetes mellitus subjects. (P value >0.05)[55].

The hypothesis that low 25(OH) D levels are associated with poorer glycemic control in diabetes mellitus (DM) patients was investigated in a prospective observational cohort study carried over 1000 type 1 and type 2 diabetes patients reported to outpatient clinics of a tertiary centre in Riyadh. Baseline HbA1c and vitamin D levels were recorded prior to supplementation and after a period of 9 months of supplementation with vitamin D. Results of the study revealed a total of 73.1% of patients having 25 (OH) D deficiency. HbA1c levels were found to be inversely correlated to 25 (OH)D levels (r = -0.14 (P=< 0.0000002). it was observed that the mean HbA1C dropped down to 7.70 form 10.55 after Vitamin D supplementation to the patients. It may be concluded based on the findings of this study that advising regular check on Vitamin D levels and correcting any deficiency would result in better blood glucose control[56].

A cross-sectional study conducted in 2016 investigated serum 25-hydroxy Vitamin D level in diabetic patients and compared it to the normal individuals. Study was conducted on a total of 106 subjects, 75 of those were free of diabetes while 31 were type 2 diabetics. Results have shown that the prevalence of Vitamin D deficiency (<50 nmol/l) was 88.87% in diabetic and 92% in normal subjects respectively which meant that level of Vitamin D was 8% lesser in diabetics in comparison to non-diabetics. However, the mean serum level of Vitamin D was not significantly different between the two groups (P=0.788). There was significant positive association of Vitamin D level with age in subjects with normal glucose levels[57].

A review paper published in 2011 summarized the relation between Vitamin D and diabetes and discussed the mechanism of action of vitamin D and its implications on health. Two main forms of Vitamin D: ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) were clinically understood, highlighting the mechanism and dietary recommendations. 2-step process of conversion in the liver and kidney for both the forms was explained. Also, authors discussed binding of active form, 1, 25-dihydroxyvitamin D to Vitamin D receptors (VDRs). This mechanism explained why diabetics having pre-existing liver and kidney are amenable to high risk of Vitamin D deficiency. Supported by observational and experimental evidence, it was concluded that Vitamin D status appears to play a role in the development as well as treatment of diabetes and reasonable supplementation of Vitamin D can possibly reduce incidence of diabetes mellitus[58].

Over the past decade, Vitamin D deficiency has been linked to an increase risk for a number of extra skeletal conditions including type to diabetes. Its antidiabetic properties have been hypothesized to be by regulating insulin secretion or its sensitivity, its anti-inflammatory effect as well as down-regulation of elevated parathyroid hormone which impair insulin secretion[59-62]. Conflicting results also suggest its role in glucose homeostasis.

Many cross-sectional studies have highlighted that insufficient Vitamin D levels was associated with type 2 diabetes and its complications[63-65]. Also low levels of Vitamin D have been observed in obesity and metabolic syndrome- the two predisposing situations for the development of diabetes[66].

Prospective cohort studies have revealed inverse association between serum 25-OH-Vitamin D and future risk of type 2 diabetes, hyperglycemia, insulin resistance and diabetic complications[67-69]. On the contrary, a meta-analysis of four prospective cohort studies suggested no association between Vitamin D and type 2 diabetes[70].

Intervention Studies

Many intervention studies conducted so far to evaluate the effect of Vitamin D supplementation on glycemic control have shown conflicting results[71-75]. Many previous meta-analyses had methodological limitations and the findings were inconsistence[76-79].

A recent systematic review and meta-analysis of randomized controlled trials on the issue of Vitamin D supplementation and its effect on glycemic control in diabetic patients found that Vitamin D supplementation may be beneficial for reduction of fasting glucose, HbA1c and insulin resistance in patients with type 2 diabetes with deficient Vitamin D status. This significant effect was especially prominent when Vitamin D was given in large doses for a short period of time[80].

Present thinking

Recently a study published highlighting that supplementation of vitamin D reduces the risk of type 2 diabetes in people with pre-diabetes. It was a systematic review and meta-analysis from three randomized clinical trials. All three trials included in analysis were randomized, double blinded and placebo controlled. Three formulations of Vitamin D were tested: Cholecalciferol 20,000iu (500 mcg) weekly, Cholecalciferol 4,000iu (100 mcg) daily or Eldecalcitol 0.75 mcg daily against placebos[81].

The results showed that Vitamin D significantly reduced the risk of developing frank diabetes by 15 percent in adjusted analysis. The three year absolute risk reduction was 33 percent. There were no differences in the rate ratios for adverse events related to vitamin D such as kidney stones, hypercalcemia and hypercalciuria as compared to placebo.

The absolute risk reduction is small when compared with the risk reduction seen with intensive life style change (58%) and with metformin administration (31%) [82]. However, when these data are extrapolated to the 374 million adults throughout the word who are pre-diabetics suggests that this simple Vitamin D supplementation could delay the onset of diabetes in more than 10 million people.

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Short Review

Hypnotherapy: A Short Review

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ABSTRACT

Hypnotherapy stands out among the many therapeutic modalities as a fascinating and multifaceted method that provides a deep dive into the complex interactions between the conscious and subconscious minds. The review aims at advancing the current understanding of hypnotherapeutic procedure for clinical problems by focusing on the research evidence and the respective methodological limitations along with the benefits of this therapy. This review provides an introductory overview of hypnotherapy, clarifying its theoretical foundations, historical antecedents, and modern uses, while highlighting its transforming potential for those seeking deep healing and personal development. Furthermore, the short review also highlights the current challenges and directions for future studies.

KEYWORDS: Theoretical foundation, Hypnotherapy, Subconscious mind, Clinical problems

INTRODUCTION

In the beginning of the review, it is important to define the two overlapping terms of hypnosis and hypnotherapy. Hypnosis can be defined as an altered state of consciousness whereas hypnotherapy is a psychotherapeutic intervention in which various techniques of hypnosis ranging from simple suggestion to psychoanalysis are utilized[1]. Clinical hypnotherapy and mindfulness hypnotherapy are such extensions used in relieving stress and other clinical conditions[2,3,4]. A considerable number of studies have shown its efficacy in a variety of clinical conditions[5]. Hypnotherapy is found to be efficacious in the management of various psychosomatic disorders[6]. In several researches, it has been recognized as a promising method for most of the functional gastro-intestinal disorders[7,8]. With respect to FGIDs, the efficacy of the hypnotherapy especially the extended intervention of gut-focused hypnotherapy has been studied most in the condition of irritable bowel syndrome[9,10,11]. It has also shown significant efficacy in pain management of palliative care services[12]. Hypnotherapy is thought to induce relaxation and bring about change in which the suggestions are predominantly used. In clinical practice hypnotic suggestions and practice has been incorporated and used in as adjunct to many therapeutic practices. One of the modifications in this area is the emergence of cognitive hypnotherapy in which hypnosis is

added with CBT techniques. It was first conducted on depressive condition which resulted in greater reduction in depressive features[13]. Subsequently it was administered to various other clinical conditions[14].

A hypnosis intervention is generally applied in clinical settings to bring the subject into a trance state. The induction of mental imagery and relaxed state are typically introduced in the initial suggestions of hypnosis process. Furthermore, majority of experts believe that relaxation is the most fundamental aspect of hypnosis, and this is known as the primer of hypnosis[15]. Oral Suggestions as are generally put forward in hypnotherapy. This communication is distinct compared to regular instructions since they are perceived by the subject as effortless and imply a successful response[16]. However, mental imagery is the tool that is employed both during induction and suggestions for improvement in which regressive, creative, concrete, or ego-strengthening suggestions are all possible[17]. With respect to normal and pathological personality traits, these were historically conceptualized to understand cluster of hypnotizability qualities in a person such as suggestibility, hypnotic susceptibility, hysterical, passivity, expectancy, fragile will, fantasy proneness, dependent and pleasing attitude[18,19]. Hypnotic susceptibility refers to an individual's ability of increased responsiveness to suggestions in order to bring about changes in his or her subjective world[20]. Furthermore, several studies have also been conducted to see their association with hypnotic suggestibility. Though the research attempts have been done in order to find the relationship between pathological personality traits and hypnosis, the explicit associations between hypnotic suggestibility and these personality traits still remain unclear[21].

The Hypnotic Odyssey through History

The history of hypnotherapy is steeped in a rich tapestry of prehistoric activities that utilized altered states of consciousness for spiritual discovery and healing. However, professional investigations into hypnosis did not begin to appear until the late 1700s. The idea of "animal magnetism," first proposed by the Austrian physician Franz Mesmer, suggested that health may be influenced by an invisible force. The field of hypnosis developed as a result of Mesmer's methods, and James Braid later named the phenomenon in the 1800s.

The emphasis was moved from the mystical to the scientific by Scottish surgeon Braid, who emphasized the ability of suggestion to induce trance-like experiences. This signified the official introduction of hypnosis as a medical modality. The historical journey of hypnotherapy shows a persistent search to comprehend and utilize the latent capacities of the human mind, from the captivating rites of ancient civilizations to the scientific scrutiny of the 19th century.

The Hypnotherapy Theoretical Landscape

Hypnotherapy is based on the fundamental idea that the subconscious mind is a storehouse of unrealized potential that shapes feelings, ideas, and actions. The hypnotic state, which is marked by increased suggestibility and concentrated attention, is a gateway to the subconscious that can be exploited to alter it.

The "state" vs. "non-state" theories are two theoretical arguments concerning hypnosis that centre on whether the phenomenon is a result of suggestion and social influence or if it entails an altered state of consciousness.

Modern hypnotherapy uses a wide range of approaches, from regression and imagery to direct suggestion, all of which are customized to meet the individual needs of each patient. It is clear from navigating this theoretical terrain that hypnotherapy is a dynamic and individualized exploration of the inner workings of the mind rather than a one-size-fits-all method.

Contemporary Uses and Upcoming Aspects

Hypnosis has evolved from its historical origins to become a multifaceted instrument with a wide range of uses in the modern era. Its effectiveness in treating ailments like anxiety, phobias, and chronic pain is supported by clinical study. Hypnotherapy has found a niche in treating lifestyle difficulties like weight management, sleep disorders, and quitting smoking, in addition to typical mental health issues. Additionally, the fusion of hypnosis with complementary therapies such as mindfulness and cognitive-behavioural therapy (CBT) demonstrates the flexibility and synergy of hypnosis within a more comprehensive holistic healing framework. As we investigate contemporary uses, it becomes clear that hypnosis is not limited to the therapeutic setting; rather, it has applications in the areas of personal growth, enhancing creativity, and optimizing human potential.

There has been a mixed history and reaction to hypnosis which originated from the Greek term "hypno" meaning sleep. Because of stage hypnotists, its reputation and reliability have been damaged and its practice has been historically linked to hysteria and witchcraft. As its history suggests almost three centuries back, hypnosis was initially referred to as mesmerism after the name famous Austrian physician Franz Mesmer which was subsequently replaced with 'animal magnetism' due to the belief that magnets might induce trances in the people. However, this was eventually refuted and in place of 'animal magnetism', Braid (1843) created the word hypnosis, which is still in use today[22]. Hypnosis can be defined as a state of subjective experience involving focused attention and reduced peripheral awareness as a response to suggestion[23]. Furthermore, in order to carry out hypnotherapy, the expert uses hypnotic induction as a major procedure to induce hypnotic state in which an individual goes through several suggested changes in his physiology and subjective experiences that is often referred to as hypnotisability. According to Mende (2009)[24], Hypnotherapy is the only therapeutic approach that uses suggestions in a systematic and planned way, even though suggestion phenomena exist outside of it. Hypnotherapy is conceptualized as a means of helping clients develop powerful personal resources that can be

purposefully directed towards achieving their therapeutic goals states[25].

In general, it is disheartening to learn that the lack of evidence-based research and the significant historical past of hypnosis and hypnotherapy may have caused the promotion and use of hypnosis to be unnecessarily delayed. But in the past fifty years, hypnosis has become a recognized, scientifically supported form of therapy. As Weisberg (2008)[26] notes, there is a substantial body of research illustrating the efficacy of hypnosis as part of integrative treatment for a number of conditions that have proven challenging for traditional medicine to treat. In the case of certain disorders (like irritable bowel syndrome), there exists sufficient evidence to support the efficacy of hypnosis that it would be unethical to withhold this form of therapy from patients. The use of hypnosis to reduce pain related to numerous invasive and diagnostic procedures is now better supported by data.

The research of Spiegel indicates that hypnotherapy has "special relevance to the assessment and treatment of anxiety disorders, including PTSD, because of its sensitizing role in enhancing the potential for mind–body control," which is further evidence that Weisberg's strong support for hypnosis as a treatment modality is beneficial[27].

Hypnotherapy in Children and Adolescents: While working with children and adolescents, the initial phase consists of a didactic session of parents' and children's previous psychological issues regarding hypnotherapy are explored[1]. Moreover, preconceived notions are also addressed and cleared up in the phase. Before offering hypnotherapy to a child, in the first phase a clinical hypnotherapist typically conducts an individual psychological assessment which is then followed by the second phase of the hypnotizability evaluation[28]. The second phase might also be seen as a practice or warm up session where the child learns about and experiences of the induction technique.

CONCLUSION

The growth of interest in hypnotherapy is reflected in its unique approach to deal with variety of stress and clinical conditions. This review summarizes the application of hypnotherapy and related cluster of personality traits which are assumed to facilitate hypnotic induction in a person. However, the association between these traits and the therapeutic approach lack empirical support in recent researches. The present review suggests that hypnotherapy is beneficial in most of the clinical conditions in relieving symptoms. However, most of the studies were found to be suffered from methodological limitations and hence more systematic researches are warranted to confirm this.

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Commentary

The Façade of Virtual Intimacy

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Karl Marx has described human beings as social animals, with an innate need for connection – physical, emotional, social, or spiritual. Even the most introverted will find themselves rooting for connections with non-human things like nature, gadgets, or books. In this context, we have witnessed a steep upward bend in the evolutional curve of human relationships with the advent of digital platforms. Facebook, Snapchat, and Instagram have revolutionized the modes and range of our interactions. Inadvertently it has revolutionized the trends of intimate relationships. Let us look closely at how internet and social media are deeply intertwined with relationships in our day-to-day lives.

Our recent tryst with the pandemic-imposed lockdown made us present to the many benefits of digitalisation; staying connected with estranged loved ones to say the least. It was evident that online connections help dampen the dullness of isolation, creating an almost surreal experience of spending time with a loved one through the video interface. It helps to bridge geographical gaps in a relationship and in most cases, save it from emotional gaps of silence or spaced conversations. We could simply appreciate how a small text or voicemail from our partner could brighten our day or make us feel like we matter.

The first things that anyone especially those seeking to form a new relationship would notice about media platforms are its attractive features and quick paced interactions. The popular filters in reels and various applications help beautify new age netizens in their desired way and make them feel comfortable in their skin. How far does this take them, is the real question though.

It would not be alarming to find that someone on the other end of a digital conversation turns out to be deceitful or fraudulent, and not who they posed as in an online profile. The nature of the interface is such, that it allows the dark side of an individual to play roles devoid of accountability or actual investment. Someone who is vulnerable and emotionally available could be the most likely target of hurt and exploitation, like meeting in non-public places or blackmail, from untrustworthy elements. It could be very easy to generate unreasonable expectations from lofty promises made online, only to find them unfulfilled. Thus, virtual reality could never replace the intuitive judgments which can be made in real life face-to-face interactions.

One also needs to consider the risk of emotional, if not actual infidelity. Digital interface could be equally hazardous for a relationship that entails one or both partners seeking ventilation. The thin line of emotional infidelity carries equivalent risks of emotional and overt trauma to an individual. It would be debatable though to understand what exactly defines infidelity on emotional grounds. The concept of loyalty and fidelity is highly subjective. On one end it reflects the deep-rooted tradition of Indian philosophy which advocates monogamy, and on another, it allows expression of a wide range of interpersonal relationships, not necessarily confined to the expression of libido or sexuality.

By nature of being human, we experience a natural physiological high on varied planes – through the gut (food-gasm), through the mind (sapiosexuals) or through the body (orgasm). A rush of dopamine is the common mechanism

behind these experiences which makes us want to experience them more. Today's world exposes the human brain to a plethora of options which entangle us into the vicious cycle of dopamine highs and lows – for example, alcohol, nicotine, heroin, cocaine, LSD, and other psychoactive drugs. To add to this list, we cannot underestimate the comparable impact of comfort foods or even internet use (screen time) on our vulnerable minds. If the role of physiological urges and the induced cravings of these new-age innovations were to be combined, one can only imagine how compelling and hazardous their effect could be.

In the midst of a surge of emotions, ruled by hormones and neurotransmitters, the primitive mind (amygdala, orbitofrontal cortex) takes over the more evolved rational and logical mind (prefrontal cortex) and illudes a person into acting on impulse. These are very challenging to resist and reason with and most likely draw a person into an addictive dependence – which by definition explains that indulgence into that particular thing/ person takes the highest priority over any other role or responsibility in life. The person may find it hard to stop him/herself and continue to engage despite acknowledging its side effects or psychological implications. At this point, the emotional dependence on a certain person or relationship can be as strong as the yearning for water in a mirage. It could easily be encapsulated into a medical model of brain dysfunction, wherein no amount of evidence or rationality would potentiate a person to abide by social/ moral/ ethical norms, rather just operate on basic instincts.

In a nutshell, digital media brings the basket of good, bad, and the ugly to our relationships, but knowing to spot red flags and draw lines to ensure safety could turn it into an advantage. The responsibility would be tremendously higher when forming new relationships online, as compared to maintaining it with someone you already trust.

New Drug Approvals

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
1.	Migraine	RizaFilm (rizatriptan) Oral Film	IntelGenx Corp.	RizaFilm (rizatriptan) is a serotonin (5-HT) 1B/1D receptor agonist (triptan) oral film formulation for the acute treatment of migraine.	April 14, 2023
2.	Stem Cell Therapy	Omisirge (omidubicel-onlv) Suspension for Infusion	Gamida Cell Ltd.	Omisirge (omidubicel-onlv) is a nicotinamide (NAM) modified allogeneic hematopoietic progenitor cell therapy for use in patients with hematologic malignancies to reduce risk of infection following stem cell transplantation.	April 17, 2023
3.	Amyotrophic Lateral Sclerosis	Qalsody (tofersen) Injection	Biogen Inc.	Qalsody (tofersen) is an antisense oligonucleotide indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.	April 25, 2023
4.	Prevention of Recurrent Clostridioides difficile Infection	Vowst (fecal microbiota spores, live-brpk) Capsules - formerly SER-109	Seres Therapeutics, Inc.	Vowst (fecal microbiota spores, live-brpk) is an oral microbiome therapeutic indicated to prevent the recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI.	April 26, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
5.	Schizophrenia	Uzedy (risperidone) Extended-Release Injectable Suspension	Teva Pharmaceuticals and MedinCell	Uzedy (risperidone) is a long-acting injectable atypical antipsychotic indicated for the treatment of schizophrenia in adults.	April 28, 2023
6.	Schizophrenia, Bipolar Disorder	Abilify Asimtufii (aripiprazole) Extended-Release Injectable Suspension	Otsuka Pharmaceutical Co., Ltd.	Abilify Asimtufii (aripiprazole) is a long-acting injectable atypical antipsychotic for the treatment of schizophrenia and bipolar I disorder.	April 27, 2023
7.	Pulmonary Arterial Hypertension	Liqrev (sildenafil citrate) Oral Suspension	CMP Pharma, Inc.	Liqrev (sildenafil citrate) is a ready-made oral liquid formulation of the approved phosphodiesterase-5 (PDE-5) inhibitor sildenafil used for the treatment of pulmonary arterial hypertension.	April 28, 2023
8.	Narcolepsy	Lumryz (sodium oxybate) Granules for Extended-Release Oral Suspension	Avadel Pharmaceuticals plc	Lumryz (sodium oxybate) is a once-nightly formulation of the approved central nervous system depressant sodium oxybate indicated for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy.	May 1, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
9.	Prevention of RSV Infection	Arexvy (respiratory syncytial virus vaccine, adjuvanted) Suspension for Intramuscular Injection	Glaxo SmithKline	Arexvy (respiratory syncytial virus vaccine, adjuvanted) is a vaccine indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.	May 3, 2023
10.	Pupillary Dilation	Mydcombi (phenylephrine hydrochloride and tropicamide) Ophthalmic Spray	Eyenovia, Inc.	Mydcombi (phenylephrine hydrochloride and tropicamide) is an alpha-1 adrenergic receptor agonist and anticholinergic fixed-combination ophthalmic spray indicated to induce mydriasis for diagnostic procedures and in conditions where short term pupil dilation is desired.	May 5, 2023
11.	Fabry Disease	Elfabrio (pegunigal-sidase alfa-iwxj) Injection	Protalix Bio Therap-eutics, Inc.	Elfabrio (pegunigalsidase alfa-iwxj) is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adults with confirmed Fabry disease.	May 9, 2023
12.	Menopausal Disorders, Hot Flashes	Veozah (fezolinetant) Tablets	Astellas Pharma Inc.	Veozah (fezolinetant) is a selective neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.	May 12, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
13.	Facial Wrinkles	Skinvive by Juvederm (hyaluronic acid and lidocaine) Injectable Gel	Abbvie	Skinvive by Juvéderm (hyaluronic acid and lidocaine) is an intradermal microdroplet injection containing a dermal filler and a local anesthetic used to improve skin smoothness of the cheeks in adults over the age of 21.	May 15, 2023
14.	Dry Eye Disease	Miebo (perfluorohexyloctane) Ophthalmic Solution - formerly NOV03	Bausch + Lomb Corporation and Novaliq	Miebo (perfluorohexyloctane) is a semifluorinated alkane indicated for treatment of the signs and symptoms of dry eye disease.	May 18, 2023
15.	Epidermolysis Bullosa	Vyjuvek (beremagene geperpavec-svdt) Topical Gel	Krystal Biotech, Inc.	Vyjuvek (beremagene-geperpavec-svdt) is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy for the treatment of wounds in patients dystrophic epidermolysis bullosa.	May 19, 2023
16.	Diffuse Large B-Cell Lymphoma	Epkinly (epcoritamab-bysp) Injection	AbbVie Inc.	Epkinly (epcoritamab-bysp) is a bispecific CD20-directed CD3 T-cell engager for use in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).	May 19, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
17.	Opioid Overdose	Opvee (nalmefene hydrochloride) Nasal Spray	Opiant Pharma-ceuticals, Inc.	Opvee (nalmefene hydrochloride) is a nasal spray formulation of the approved opioid antagonist nalmefene hydrochloride for use in the treatment of opioid overdose.	May 22, 2023
18.	Opioid Use Disorder	Brixadi (buprenorphin e) Extended-Release Injection	Braeburn Inc.	Brixadi (buprenorphine) is a partial opioid agonist for use in the treatment of opioid use disorder.	May 23, 2023
19.	Acinetobacter Pneumonia	Xacduro (sulbactam and durlobactam (co-packaged)) Kit for Injection	Innoviva, Inc.	Xacduro (sulbactam and durlobactam) is a co-packaged product containing the beta-lactam antibacterial sulbactam, and the beta lactamase inhibitor durlobactam for use in the treatment of serious infections caused by Acinetobacter.	May 23, 2023
20.	Rheumatoid arthritis, Juvenile idiopathic arthritis, Psoriatic arthritis, Ankylosing spondylitis, Crohn's disease, Ulcerative colitis, Plaque psoriasis, and Hidradenitis suppurativa.	Yuflyma (adalimumab-aaty) Injection	Celltrion USA	Yuflyma (adalimumab-aaty) is a tumor necrosis factor (TNF) blocker biosimilar to Humira, approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, and hidradenitis suppurativa.	May 23, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
21.	COVID-19	Paxlovid (nirmatrelvir and ritonavir) Tablets (co-packaged)	Pfizer Inc.	Paxlovid (nirmatrelvir and ritonavir) is a co-packaged product containing nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and ritonavir, a HIV-1 protease inhibitor and CYP3A inhibitor, indicated for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.	May 25, 2023
22.	Positron Emission Tomography Imaging, Diagnosis and Investigation	Posluma (flotufolastat F 18) Injection	Blue Earth Diagnostics	Posluma (flotufolastat F 18) a radioactive diagnostic agent used for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.	May 25, 2023
23.	Heart Failure	Inpefa (sotagliflozin) Tablets	Lexicon Pharma-ceuticals, Inc.	Inpefa (sotagliflozin) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor used in the treatment of heart failure.	May 26, 2023
24.	Dry Eye Disease	Vevye (cyclosporine) Ophthalmic Solution - formerly CyclASol	Novaliq	Vevye (cyclosporine) is a calcineurin inhibitor immunosuppressant indicated for the treatment of the signs and symptoms of dry eye disease.	May 30, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
25.	Respiratory Syncytial Virus	Abrysvo (respiratory syncytial virus vaccine) Injection	Pfizer, Inc.	Abrysvo (respiratory syncytial virus vaccine) is a vaccine used for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV).	May 31, 2023
26.	Diffuse Large B-Cell Lymphoma	Columvi (glofitamab-gxbm) Injection	Genentech	Columvi (glofitamab-gxbm) is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.	June 15, 2023
27.	Bowel Preparation	Suflave (polyethylene glycol 3350, sodium sulfate, potassium chloride, magnesium sulfate, and sodium chloride) Powder for Oral Solution	Braintree Laboratories, Inc.	Suflave (polyethylene glycol 3350, sodium sulfate, potassium chloride, magnesium sulfate, and sodium chloride) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.	June 15, 2023
28.	Cardiovascular Risk Reduction	Lodoco (colchicine) Tablets	AGEPHA Pharma USA, LLC	Lodoco (colchicine) is an alkaloid indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease.	June 16, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
29.	Myasthenia Gravis	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) Injection	Halozyme Therapeutics, Inc.	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) is a neonatal Fc receptor blocker and endoglycosidase combination indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.	June 20, 2023
30.	Duchenne Muscular Dystrophy	Elevidys (delandistrogene moxeparvovec-rokl) Suspension for Intravenous Infusion	Sarepta Therapeutics, Inc.	Elevidys (delandistrogene moxeparvovec-rokl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.	June 22, 2023
31.	Alopecia	Litfulo (ritlecitinib) Capsules	Pfizer Inc.	Litfulo (ritlecitinib) is a covalent kinase inhibitor indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older.	June 23, 2023
32.	Myasthenia Gravis	Rystiggo (rozanolixizumab-noli) Injection	UCB	Rystiggo (rozanolixizumab-noli) is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) or antimuscle-specific tyrosine kinase (MuSK) antibody positive.	June 26, 2023

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
33.	Pediatric Growth Hormone Deficiency	Ngenla (somatrogon-ghla) Injection	Pfizer Inc.	Ngenla (somatrogon-ghla) is a long-acting human growth hormone analog used for the treatment of pediatric growth hormone deficiency.	June 27, 2023
34.	Diabetes, Type 1	Lantidra (donislecel-jujn) Cellular Suspension for Infusion	CellTrans, Inc.	Lantidra (donislecel-jujn) is an allogeneic pancreatic islet cellular therapy for the treatment of type 1 diabetes mellitus in adults whose symptoms are not well controlled.	June 28, 2023
35.	Hemophilia A	Roctavian (valocto-cogene roxapar-vovec-rvox) Suspension for Intravenous Infusion	BioMarin Pharma-ceutical Inc.	Roctavian (valoctocogene-roxaparvovec-rvox) is an adeno-associated virus vector-based gene therapy for the treatment of adults with severe hemophilia A.	June 29, 2023

(Ravindra Bangar)
Editor

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In particular situations, where the referees disagree considerably about the quality of a manuscript, there are a number of strategies for reaching a decision. When the editor receives positive and negative reviews for the same manuscript by two different reviewers, the editor will ask for one or more additional reviews or on the basis of comments of one reviewer, the edit may take his/her decision about the respective manuscript.

Reviewers' Guidelines

ETHICS AND RESPONSIBILITY

We are committed to upholding the integrity of the work we publish. Pacific Journal of Medical and Health Sciences takes issues of copyright infringement, plagiarism or other breaches of best practice in publication very seriously. We seek to protect the rights of our authors and we always investigate claims of plagiarism or misuse of published articles. Equally, we seek to protect the reputation of our journal against malpractice. Submitted articles may be checked with duplication-checking software. Where an article is found to have plagiarized other work or included third-party copyright material without permission or with insufficient acknowledgement, or where the authorship of the article is contested, we reserve the right to take action including, but not limited to: publishing an erratum or corrigendum (correction); retracting the article (removing it from the journal); taking up the matter with the Head of Department or Dean of the author's institution and/or relevant academic bodies or societies; banning the author from publication in the journal in question or appropriate legal action.

We recommend that if reviewers suspect any of the following problems with any article that they are reviewing that they contact the journal editor to discuss the situation without delay. Reviewers should keep all information about such matters confidential and not discuss them with colleagues other than the journal editor.

1. If you suspect that the paper has been either published or submitted to another journal.
2. If you suspect that the paper is duplicating the work of others.
3. If you suspect that there might be problems with the ethics of the research conducted.
4. If you suspect that there might be an undeclared conflict of interest attached to the paper (Editors might have more information about this than you do so it is best to check).

We recommend that reviewers should think carefully about their own potential conflicts of interest relating to the paper before undertaking the review. They should also notify the editor if they become aware of the identity of the author during blind peer review. Additionally, reviewers should be careful not to make judgments about the paper based on personal, financial, intellectual biases or any other considerations than the quality of the research and written presentation of the paper.

PURPOSE OF PEER REVIEW

It is widely accepted that Peer Review is the most valid form of research evaluation and it is a cornerstone in the process of bringing academic research to publication in the following ways:

Evaluation - Peer review is an effective form of research evaluation to help select the highest quality articles for publication.

Integrity - Peer review ensures the integrity of the publishing process and the scholarly record. Reviewers are independent of journal publications and the research being conducted.

Quality - The filtering process and revision advice improve the quality of the final research article as well as offering the author new insights into their research methods and the results that they have compiled. Peer review gives authors access to the opinions of experts in the field who can provide support and insight.

TYPE OF PEER REVIEW OF JOURNAL

Double blind peer review - names are hidden from both reviewers and the authors.

HOW TO REVIEW ARTICLES

Referees are sent invitations to review papers by journal editors. These requests are made via email. If you are asked to provide a review, in order to avoid delays, we would be grateful if you could let us know as soon as possible if you are unable to complete it at the time or if a problem arises after the invitation has been accepted. Suggestions for alternative reviewers are always gratefully received!

Below we present some advice and guidance about how to conduct a review and put together a reviewer report that will be effective and beneficial to authors:

ETIQUETTE

Timeliness - We understand that our reviewers are busy so it won't always be possible for invitations to be accepted. Please let us know as soon as possible if they need to refuse a review or if a problem arises after the invitation has been accepted. Most journal editors are grateful to receive suggestions about someone else that might be suitable to do the review if you have to decline the invitation.

Conflict of Interest - it is important to highlight to the journal editor any conflict of interest that you feel might occur if you review the paper. Please do so as discretely and as quickly as possible.

Discussion -- it is important to discuss with the journal editor any concerns that you have about the paper or their specific requirements for review if you are being invited to review for the first time. Editors are usually open to discussing their expectations and journal requirements with reviewers.

Ethics -Refer ethics and responsibility related to peer review.

INDIVIDUAL JOURNAL REVIEWER GUIDELINES

These guidelines include a list of questions and will usually offer the reviewer the chance to make general comments

- Read the paper very carefully.
- Relevance to the publication (most editors will reject at submission those articles that do not match the aims and scope of the journal, but it is worth considering this as you read the paper).
- Significance of the research within the field.
- Originality of the work conducted. It is also important to consider whether the author has ever published a substantially similar paper elsewhere (if you suspect the work may not be original, please view our ethics page for information about how to deal with a variety of situations).
- The methodology employed during the research.
- Technical accuracy.

STRUCTURE AND COMMUNICATION

- Accuracy of references
- Overall Structure of the paper, communication of main points and flow of argument
- Quality of written language and structure of the article
- Effectiveness of the article abstract and introduction (some journals will request
- Whether the argument is clear and logical and the conclusions presented are supported by the results or evidence presented
- Whether the title of the article is suitable or effective
- Whether the abstract is a good summary of the article
- Whether the work meets with the article types accepted by the journal

The accessibility of the paper to a broad readership

Whether the paper is internally consistent

FEEDBACK IN YOUR REVIEWER REPORT - GIVING ADVICE TO AUTHORS AND SUGGESTING REVISIONS

- Be as objective as possible in your comments and criticisms and avoid making negative comments about work referenced in the article

- Be specific and as constructive as possible in your criticism. Be clear about what needs to be added or revised.
- If relevant, make suggestions about additional literature that the author might read to enrich or improve their arguments
- You should ensure that you are clear which of your comments you are happy for the author to see and which are meant specifically for the journal editor in order to avoid confusion or bad feeling
- While peer reviewers should feel free to make general comments on written quality and make suggestions about how articles might be improved by broadening reading of other literature, it is not the job of the peer reviewer to rewrite articles or suggest detailed changes to wording

MAKING A DECISION

> Recommend whether a paper should be accepted, rejected or revised (major or minor revisions)

> Most importantly, keep all activity, content and comments relating to the paper confidential

Most important - keep all activity, content and comments relating to the paper confidential.

Publication Ethics and Publication Malpractice Statement

Our publication ethics and publication malpractice statement is mainly based on the Code of Conduct and Best-Practice Guidelines for Journal Editors (Committee on Publication Ethics, 2011).

EDITORS' RESPONSIBILITIES

Publication Decisions

The editor is responsible for deciding which of the papers submitted to the journal will be published. The editor will evaluate manuscripts without regard to the authors' race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy. The decision will be based on the paper's importance, originality and clarity, and the study's validity and its relevance to the journal's scope. Current legal requirements regarding libel, copyright infringement, and plagiarism should also beconsidered.

Confidentiality

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and Conflicts of Interest

Unpublished materials disclosed in a submitted paper will not be used by the editor or the members of the editorial board for their own research purposes without the author's explicit written consent.

REVIEWERS' RESPONSIBILITIES

Contribution to Editorial Decisions

The peer-reviewing process assists the editor and the editorial board in making editorial decisions and may also serve the author in improving the paper.

Promptness

Any selected referee who feels unqualified to review the research reported in manuscript or knows that its prompt review will be impossible should notify the editor and withdraw from the review process.

Confidentiality

Any manuscripts received for review must be treated as confidential documents. They must not be disclosed to or discussed with others except as authorized by the editor.

Standards of Objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Disclosure and Conflict of Interest

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage. Reviewers should not consider manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or institutions associated with the papers.

AUTHORS' DUTIES

Reporting Standards

Authors of original research reports should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable.

Originality, Plagiarism and Acknowledgement of Sources

Authors will submit only entirely original works, and will appropriately cite or quote the work and/or words of others. Publications that have been influential in determining the nature of the reported work should also be cited.

Multiple, Redundant or Concurrent Publication

In general, papers describing essentially the same research should not be published in more than one journal. Submitting the same paper to more than one journal constitutes unethical publishing behavior and is unacceptable. Manuscripts which have been published as copyrighted material elsewhere cannot be submitted. In addition, manuscripts under review by the journal should not be resubmitted to copyrighted publications. However, by submitting a manuscript, the author(s) retain the rights to the published material.

Authorship of the Paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. The corresponding author ensures that all contributing co-authors and no uninvolved persons are included in the author list. The corresponding author will also verify that all co-authors have approved the final version of the paper and have agreed to its submission for publication. Disclosure and conflicts of interest

All authors should include a statement disclosing any financial or other substantive conflicts of interest that may be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and to cooperate with the editor to retract or correct the paper in form of an erratum.

Disclaimer

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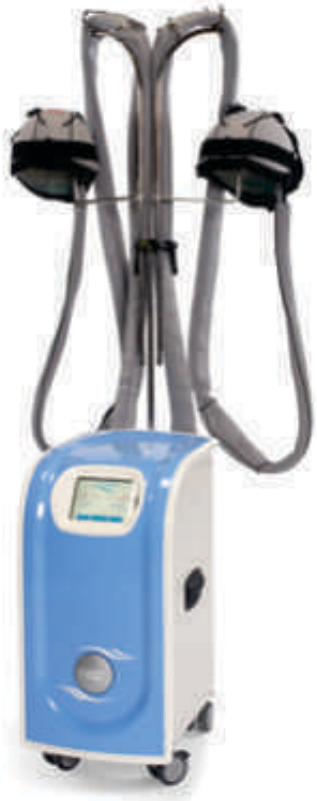
DEPARTMENT OF ONCOLOGY

SCALP COOLING MACHINE



Rajasthan's First Scalp Cooling Machine has been established in Pacific Medical College and Hospital, Udaipur for providing US FDA Approved Scalp Cooling Therapy to Cancer Patients to prevent hair-loss due to Chemotherapy.

PACIFIC IVF CENTER

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