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Stress, Platelet Aggregation, and Cardiovascular Risk: A Complex Interplay

In the modern era, stress is often considered a ubiquitous part of life. The relentless pace of work, societal pressures, and personal responsibilities has led to increased stress levels for most individuals. While stress has long been recognized for its psychological and emotional impacts, its physiological effects, particularly on cardiovascular health, are gaining significant attention. In the research paper of this issue we explore the intricate relationship between stress, platelet aggregation, and cardiovascular risk, shedding light on how these factors interplay and contribute to cardiovascular disease. We also delve into the current understanding of this complex interplay, focusing on healthy individuals, patients with ischemic heart disease (IHD), type 2 diabetes mellitus (T2DM), and those with a combination of these conditions.

Stress and Platelet Aggregation: A Primer

Stress, a pervasive component of human life, is a complex physiological response to perceived threats or challenges. While it is essential for survival, chronic or excessive stress can have detrimental effects on various physiological systems. One such system is the cardiovascular system, where stress can influence platelet aggregation, a crucial process in hemostasis and thrombosis.

Platelets, tiny cell fragments in the blood, play a pivotal role in maintaining blood clotting. When a blood vessel is injured, platelets adhere to the damaged area and aggregate to form a clot, preventing excessive blood loss. However, under certain conditions, platelets can become hyperactive, leading to the formation of unwanted clots that can block blood vessels and cause heart attacks or strokes.

The intricate relationship between stress and platelet aggregation involves a complex interplay of neuroendocrine, immune, and vascular factors. When an individual perceives a stressor, the hypothalamus-pituitary-adrenal (HPA) axis is activated, leading to the release of stress hormones such as cortisol and adrenaline. These hormones trigger a cascade of physiological changes, including increased heart rate, blood pressure, and blood sugar levels.

One of the key effects of stress hormones is the activation of the sympathetic nervous system, which stimulates platelet production and release from the bone marrow. Additionally, stress hormones can directly induce platelet activation by increasing intracellular calcium levels and promoting the release of platelet-derived growth factor (PDGF) and other prothrombotic substances.

Furthermore, stress can trigger an inflammatory response, leading to the release of cytokines and other inflammatory mediators. These inflammatory substances can enhance platelet reactivity by upregulating platelet receptors and promoting the expression of procoagulant proteins. Furthermore, chronic stress can impair endothelial function, the inner lining of blood vessels. Endothelial dysfunction is characterized by reduced nitric oxide production, which normally inhibits platelet aggregation and promotes vasodilation.

The combination of platelet hyperactivity, increased platelet production, and endothelial dysfunction creates a prothrombotic state, increasing the risk of cardiovascular events. Studies have shown that individuals with high levels of stress are more likely to experience heart attacks, strokes, and other thrombotic complications.

It is important to note that the impact of stress on platelet aggregation can vary among individuals. Factors such as genetic predisposition, lifestyle, and underlying medical conditions can influence an individual's susceptibility to stress-induced platelet activation. Additionally, the duration and intensity of stress play a crucial role in determining the magnitude of its effects on platelet function.

Understanding the mechanisms by which stress influences platelet aggregation is essential for developing effective strategies to prevent and manage cardiovascular disease. Stress management techniques, such as relaxation exercises, meditation, and physical activity, can help to reduce stress levels and improve cardiovascular health. Additionally, lifestyle modifications, including a healthy diet, regular exercise, and adequate sleep, can contribute to overall well-being and reduce the risk of stress-related platelet activation.

The complex interplay between stress and platelet aggregation highlights the importance of addressing stress as a modifiable risk factor for cardiovascular disease. By understanding the underlying mechanisms and implementing effective stress management strategies, individuals can take proactive steps to protect their cardiovascular health.

The Link between Stress and Platelet Aggregation

Recent research has increasingly highlighted the connection between stress and platelet aggregation. Stress-induced changes in platelet function can significantly impact cardiovascular risk. The mechanisms through which stress affects platelet aggregation are multifaceted and involve several physiological and biochemical processes.

- **Hormonal Influence**: Stress hormones, particularly cortisol and adrenaline, can directly affect platelet function. Cortisol can enhance platelet reactivity by increasing the expression of adhesion molecules and amplifying platelet activation. Adrenaline, on the other hand, can stimulate platelet aggregation through β-adrenergic receptors.
- **Inflammation**: Chronic stress is associated with increased systemic inflammation. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can enhance platelet activation and aggregation. These inflammatory mediators promote a pro-thrombotic state, increasing the likelihood of clot formation and cardiovascular events.
- **Endothelial Dysfunction**: Stress can lead to endothelial dysfunction, characterized by impaired endothelial cell function and reduced nitric oxide (NO) production. The endothelium plays a critical role in regulating platelet aggregation by releasing anti-thrombotic factors such as NO and prostacyclin. Endothelial dysfunction can thus lead to increased platelet aggregation and heightened cardiovascular risk.
- **Sympathetic Nervous System Activation**: Chronic stress leads to persistent activation of the sympathetic nervous system, which can enhance platelet activation through adrenergic signaling. This heightened platelet reactivity can contribute to increased risk of thrombotic events.

Stress and Platelet Aggregation in Healthy Individuals

The intricate relationship between stress and platelet aggregation is a complex interplay of physiological responses that has significant implications for cardiovascular health. While the impact of stress on platelet function is a subject of ongoing research, evidence suggests that acute and chronic stress can influence platelet behavior in healthy individuals.

Platelets, small cell fragments in the blood, play a crucial role in hemostasis, the process of blood clotting. When a blood vessel is injured, platelets adhere to the damaged area and aggregate to form a clot, preventing excessive blood loss. However, under certain conditions, platelets can become hyperactive, leading to the formation of unwanted clots that can block blood vessels and cause heart attacks or strokes.

Stress, a physiological response to perceived threats or challenges, activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. This activation leads to the release of stress hormones such as adrenaline (epinephrine) and cortisol. These hormones induce a cascade of physiological changes, including increased heart rate, blood pressure, and blood sugar levels.

Several mechanisms link stress to platelet activation. Adrenaline, a potent vasoconstrictor, can directly stimulate platelet aggregation by binding to specific receptors on platelet membranes. Cortisol, while primarily known for its anti-inflammatory effects, can also influence platelet function. Although the exact mechanisms are not fully understood, cortisol is believed to enhance platelet sensitivity to other agonists, such as adrenaline and thromboxane A2.

Acute stress, such as public speaking or physical exercise, can trigger a transient increase in platelet activity. These changes are often adaptive and necessary for maintaining hemostasis during periods of heightened physical exertion. However, the magnitude of platelet activation in response to acute stress can vary among individuals, depending on factors such as stress reactivity, genetic predisposition, and lifestyle.

Chronic stress, on the other hand, can have more sustained effects on platelet function. Prolonged exposure to stress hormones can lead to desensitization of platelet receptors, resulting in a compensatory increase in platelet reactivity. Additionally, chronic stress can contribute to inflammation, which is associated with increased platelet activation. Inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, can enhance platelet responsiveness to various stimuli.

It is important to note that the impact of stress on platelet aggregation is influenced by various factors, including gender, age, and lifestyle. Some studies suggest that women may be more susceptible to stress-induced platelet activation, although the underlying mechanisms are not fully understood. Additionally, older adults may experience a blunted platelet response to acute stress, possibly due to age-related changes in platelet function.

Lifestyle factors, such as smoking, excessive alcohol consumption, and unhealthy diet, can exacerbate the effects of stress on platelet aggregation. These factors contribute to oxidative stress, inflammation, and endothelial dysfunction, creating a prothrombotic environment.

The relationship between stress and platelet aggregation in healthy individuals is complex and multifaceted. While acute stress typically induces transient platelet activation, chronic stress can have more sustained effects on platelet function. Lifestyle modifications, stress management techniques, and regular health check-ups can help mitigate the negative impact of stress on platelet activity and overall cardiovascular health.

Stress and Platelet Aggregation in Patients with Ischemic heart disease (IHD)

Ischemic heart disease (IHD) is a chronic condition characterized by the narrowing of coronary arteries, reducing blood flow to the heart. This condition is a leading cause of morbidity and mortality worldwide, and its pathophysiology involves a complex interplay of various factors, including stress and platelet aggregation.

Platelets, small cell fragments in the blood, play a crucial role in hemostasis, the process of blood clotting. While essential for preventing excessive bleeding, hyperactive platelets can contribute to thrombus formation, which can occlude coronary arteries and lead to acute coronary syndromes such as myocardial infarction.

Stress, a physiological response to perceived threats or challenges, is a well-established risk factor for IHD. Chronic stress activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of stress hormones like adrenaline (epinephrine) and cortisol. These hormones can directly and indirectly influence platelet function.

Adrenaline, a potent vasoconstrictor, can stimulate platelet activation by binding to specific receptors on platelet membranes. This interaction triggers a cascade of intracellular signaling events, leading to platelet shape change, granule release, and aggregation. Cortisol, while primarily known for its anti-inflammatory effects, can also enhance platelet reactivity. It has been suggested that cortisol may increase platelet sensitivity to other agonists, such as adrenaline and thromboxane A2.

Furthermore, stress can induce an inflammatory response, leading to the release of cytokines and other inflammatory mediators. These inflammatory substances can promote platelet activation and aggregation by upregulating platelet receptors and enhancing the expression of procoagulant proteins. Chronic inflammation is a hallmark of IHD and can contribute to plaque formation and destabilization.

In patients with IHD, the combination of chronic stress, platelet hyperactivity, and endothelial dysfunction creates a prothrombotic environment, increasing the risk of acute coronary events. Stress-induced platelet activation can exacerbate myocardial ischemia by reducing coronary blood flow and promoting thrombus formation. Additionally, stress can trigger plaque rupture, leading to the formation of a coronary thrombus that can completely occlude a coronary artery.

Several studies have demonstrated the association between stress and platelet activation in patients with IHD. Treadmill stress tests (TMT) have shown that acute stress can induce significant increases in platelet aggregation in these patients. Furthermore, psychological stress, as assessed by self-reported measures, has been linked to increased platelet reactivity.

It is important to note that the impact of stress on platelet aggregation in patients with IHD can vary depending on the severity of the disease, the presence of comorbidities, and individual factors. Patients with unstable angina or recent myocardial infarction may be particularly susceptible to stress-induced platelet activation.

Managing stress is a crucial component of the comprehensive care of patients with IHD. Stress reduction techniques, such as relaxation exercises, meditation, and cognitive-behavioral therapy, can help to reduce platelet reactivity and lower the risk of acute coronary events. Additionally, lifestyle modifications, including regular physical activity, a healthy diet, and adequate sleep, can contribute to overall well-being and improve cardiovascular health.

The interplay between stress and platelet aggregation plays a significant role in the pathophysiology of IHD. By understanding the mechanisms underlying this complex relationship,

healthcare providers can implement effective strategies to manage stress and reduce the risk of adverse cardiovascular events in patients with IHD.

Stress and Platelet Aggregation in Patients with Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. It is a major public health concern globally, with a burgeoning prevalence and associated with a significantly elevated risk of cardiovascular disease (CVD).Central to this increased CVD risk is the interplay between hyperglycemia, inflammation, endothelial dysfunction, and platelet hyperactivity. This essay will explore the intricate relationship between stress and platelet aggregation in the context of T2DM.

Platelets, small cell fragments in the blood, play a crucial role in hemostasis, the process of blood clotting. However, hyperactive platelets can contribute to thrombus formation, leading to cardiovascular events. T2DM patients exhibit increased platelet reactivity compared to healthy individuals, a phenomenon attributed to several factors, including hyperglycemia, oxidative stress, and inflammation.

Stress, a physiological response to perceived threats or challenges, is a common comorbidity in T2DM.It can exacerbate the hypercoagulable state by influencing platelet function. The activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis in response to stress leads to the release of stress hormones like adrenaline and cortisol. These hormones can directly stimulate platelet activation and aggregation.

Hyperglycemia, a hallmark of T2DM, is a potent trigger for platelet hyperactivity. Elevated glucose levels induce oxidative stress, leading to the generation of reactive oxygen species (ROS).These highly reactive molecules can damage cellular components, including platelets, and promote platelet activation. Additionally, hyperglycemia can impair nitric oxide (NO) production, a potent vasodilator and inhibitor of platelet aggregation. This endothelial dysfunction further contributes to a prothrombotic state.

Chronic inflammation is another key factor linking T2DM, stress, and platelet hyperactivity. Low-grade inflammation is prevalent in T2DM and is characterized by elevated levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). These inflammatory mediators can directly activate platelets and enhance their responsiveness to other agonists. Furthermore, stress can exacerbate inflammation, creating a vicious cycle that promotes platelet hyperactivity.

The combined effects of hyperglycemia, oxidative stress, inflammation, and stress create a prothrombotic milieu in T2DM patients, increasing the risk of cardiovascular events. Platelet hyperactivity, in conjunction with other cardiovascular risk factors such as dyslipidemia and hypertension, accelerates atherosclerosis progression and plaque instability.

Managing stress is crucial in the prevention and management of cardiovascular complications in T2DM patients. Stress reduction techniques, including relaxation exercises, meditation, and cognitive-behavioral therapy, can help to mitigate the adverse effects of stress on platelet function. Additionally, optimal glycemic control is essential to reduce platelet hyperactivity and prevent the development of diabetic complications.

The interplay between stress and platelet aggregation is a significant contributor to the increased cardiovascular risk in T2DM patients. Understanding the underlying mechanisms is essential for developing effective preventive and therapeutic strategies. By addressing both stress and metabolic control, healthcare providers can improve cardiovascular outcomes in this vulnerable

population.

Stress, Platelet Aggregation, and the Overlap of IHD and T2DM

The convergence of ischemic heart disease (IHD) and type 2 diabetes mellitus (T2DM) presents a formidable challenge to public health. Both conditions are independently associated with increased cardiovascular risk, and their coexistence significantly amplifies this risk. Central to the pathophysiology of both diseases is the role of platelet aggregation, a process intricately linked to stress.

Platelets, small cell fragments in the blood, are crucial for hemostasis, the process of blood clotting. However, their hyperactivation can lead to thrombus formation, obstructing blood flow and causing heart attacks or strokes. In the context of IHD and T2DM, platelet hyperactivity is exacerbated by a complex interplay of factors, including hyperglycemia, insulin resistance, inflammation, and oxidative stress.

Stress, a physiological response to perceived threats or challenges, is a potent trigger for platelet activation. The activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis leads to the release of stress hormones, such as adrenaline and cortisol. These hormones can directly stimulate platelet aggregation and amplify the effects of other platelet agonists.

In patients with IHD, chronic stress can contribute to plaque destabilization and thrombus formation. The combination of stress-induced platelet hyperactivity and endothelial dysfunction, a common feature of IHD, creates a prothrombotic environment. Acute stress events, such as public speaking or physical exertion, can trigger transient increases in platelet activity, potentially precipitating myocardial ischemia.

T2DM patients also exhibit increased platelet reactivity due to hyperglycemia, insulin resistance, and chronic inflammation. Stress exacerbates these conditions, leading to further platelet activation. The hyperglycemic environment promotes oxidative stress, which damages platelets and enhances their responsiveness to aggregating agents. Additionally, stress-induced inflammation can amplify the prothrombotic state in T2DM patients.

When IHD and T2DM coexist, the cardiovascular risk is dramatically elevated. The synergistic effects of these conditions on platelet function are particularly pronounced. The combined impact of hyperglycemia, insulin resistance, inflammation, and stress creates a hypercoagulable state that predisposes individuals to acute coronary events. Platelet hyperactivity, in conjunction with other cardiovascular risk factors, accelerates atherosclerosis progression and increases the likelihood of plaque rupture and thrombus formation.

Managing stress is crucial for patients with IHD and T2DM. Stress reduction techniques, such as relaxation exercises, meditation, and cognitive-behavioral therapy, can help to mitigate the adverse effects of stress on platelet function. Additionally, lifestyle modifications, including regular physical activity, a healthy diet, and adequate sleep, are essential for overall well-being and cardiovascular health.

Optimal glycemic control is another cornerstone of managing the cardiovascular risk associated with IHD and T2DM. Achieving and maintaining target blood glucose levels can help to reduce platelet hyperactivity and slow the progression of atherosclerosis. Antiplatelet therapy, such as aspirin or clopidogrel, is often prescribed to prevent platelet aggregation and reduce the risk of ischemic events.

The interplay between stress, platelet aggregation, IHD, and T2DM underscores the importance of a comprehensive approach to cardiovascular risk management. By addressing both the metabolic and psychological aspects of these conditions, healthcare providers can significantly improve patient outcomes and reduce the burden of cardiovascular disease.

Clinical Implications

The complex interplay between stress and platelet aggregation has profound clinical implications. Understanding this relationship is essential for developing effective strategies for prevention, diagnosis, and management of cardiovascular diseases.

Platelet aggregation, a critical component of hemostasis, involves the clumping of platelets to form a clot, preventing excessive bleeding. However, when dysregulated, it can contribute to thrombosis, a primary cause of acute coronary syndromes and stroke. Stress, a physiological response to perceived threats, triggers the release of stress hormones, such as adrenaline and cortisol, which can significantly impact platelet function.

In healthy individuals, acute stress can induce transient platelet activation, which is generally adaptive. However, chronic stress can lead to sustained platelet hyperactivity, increasing the risk of thrombotic events. This has significant implications for individuals with risk factors for CVD, such as hypertension, dyslipidemia, and obesity.

For patients with IHD, the combination of stress and platelet hyperactivity is particularly concerning. Stress can exacerbate myocardial ischemia by inducing vasoconstriction and increasing platelet aggregation. Furthermore, it can contribute to plaque destabilization and thrombus formation, leading to acute coronary syndromes. Therefore, stress management is a crucial component of secondary prevention in IHD patients.

In patients with type 2 diabetes mellitus (T2DM), the interplay between stress and platelet aggregation is even more complex. Hyperglycemia, insulin resistance, and chronic inflammation create a prothrombotic environment, and stress further amplifies these factors. This increased platelet reactivity significantly contributes to the elevated cardiovascular risk in T2DM patients.

The clinical implications of stress and platelet aggregation extend beyond the prevention of acute coronary events. These factors also influence the outcomes of various cardiovascular interventions. For instance, patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) may experience increased platelet reactivity during the procedure, elevating the risk of stent thrombosis or graft occlusion. Similarly, stress management is crucial for patients with atrial fibrillation, as it can reduce the risk of stroke by lowering the incidence of thrombus formation.

Several clinical strategies can be employed to mitigate the adverse effects of stress and platelet aggregation. Stress management techniques, including relaxation exercises, meditation, and cognitive-behavioral therapy, are essential for reducing platelet reactivity and improving overall cardiovascular health. Lifestyle modifications, such as regular physical activity, a healthy diet, and weight management, also play a crucial role in managing stress and reducing cardiovascular risk.

Antiplatelet therapy is a cornerstone of treatment for patients with IHD and other cardiovascular diseases. Aspirin and P2Y12 inhibitors, such as clopidogrel, ticagrelor, and prasugrel, are commonly used to inhibit platelet aggregation. However, the optimal duration of antiplatelet therapy and the balance between bleeding risk and ischemic risk require careful consideration.

Early identification of individuals at high risk for stress-related platelet hyperactivity is crucial. This can be achieved through a comprehensive assessment of cardiovascular risk factors, including stress levels, and the use of platelet function tests when indicated. By implementing preventive measures and tailoring treatment strategies to individual patient characteristics, healthcare providers can significantly reduce the burden of cardiovascular disease.

By addressing both stress and platelet function, healthcare providers can improve patient outcomes and reduce the risk of adverse cardiovascular events.

Future Directions and Research

While significant progress has been made in understanding the relationship between stress, platelet aggregation, and cardiovascular risk, several areas warrant further research:

1. **Mechanistic Insights**: More detailed studies are needed to elucidate the specific mechanisms through which stress affects platelet function. Understanding the molecular pathways involved could lead to targeted interventions to modulate platelet reactivity.
2. **Longitudinal Studies**: Long-term studies examining the impact of chronic stress on platelet aggregation and cardiovascular outcomes are essential. Such research can provide valuable insights into the cumulative effects of stress on cardiovascular health over time.
3. **Personalized Interventions**: Investigating how individual differences, such as genetic predispositions and personal stress coping styles, influence the relationship between stress and platelet aggregation can help in developing personalized stress management strategies.
4. **Integrative Approaches**: Exploring integrative approaches that combine stress management with other cardiovascular risk reduction strategies may offer comprehensive solutions for improving cardiovascular health.

The interplay between stress, platelet aggregation, and cardiovascular risk underscores the complexity of cardiovascular disease. Stress is a significant modifiable risk factor that influences platelet function and overall cardiovascular health. Understanding the mechanisms through which stress affects platelet aggregation can lead to more effective strategies for managing cardiovascular risk. Incorporating stress management techniques into cardiovascular risk reduction efforts can help mitigate the adverse effects of stress, improve overall well-being, and reduce the burden of cardiovascular disease. As research continues to evolve, a holistic approach that integrates stress management with other health-promoting strategies will be essential for addressing the multifaceted nature of cardiovascular risk.

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Research Paper

Platelet Aggregation Response to Physical Stress in Different Subsets of Individuals

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ABSTRACT

The present study was conducted to evaluate the effect of stress (TMT) on the platelet aggregation in healthy individuals, patients with IHD, patients with type 2 diabetes mellitus and patients with both IHD and diabetes mellitus. Forty persons were selected, 10 for each group. They were subjected to TMT after due consent, and blood samples were collected initially and after TMT. The blood samples were analysed for platelet aggregation using ADP and collagen as agonists.

It was observed that in healthy individuals, stress reduced platelet aggregation by around 20% and 21% induced by ADP and collagen respectively, which were statistically significant ($p<0.05$). In patients with IHD, physical stress significantly increased platelet aggregation induced by ADP by about 29% ($p<0.001$) and by collagen it increased by around 45% ($p<0.01$).Surprisingly, stress (TMT) did not affect platelet aggregation induced by ADP and collagen significantly (P=NS) in diabetic patients. Interestingly, in patients with type 2 diabetes mellitus who had associated IHD, the platelet aggregation increased around 9 percent induced by ADP ($p<0.05$) and around 11 percent induced by collagen($p<0.05$) after TMT. Both were statistically significant.

KEYWORDS: Stress, IHD, Diabetes, Aggregating agents, Light transmittance aggregometry

INTRODUCTION

The burden of atherothrombotic vascular 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. Atherothrombosis is the result of multiple complex cascade of interaction among the endogenous cells of the arterial wall, the focal hemodynamic 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, catecholamine, 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 haemostasis; 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[1-2]. 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[3-4]. For platelets to interact with the endothelium, the platelet glycoprotein 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 A2 (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", contains β-TG (Beta - thromboglobulin), PF-4 (Platelet factor four), PDGF (Platelet Derived Growth Factor) and 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. "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 PGI_2 inhibits platelet aggregation and stimulates vasodilation. The action is mediated by an increase of platelet cAMP and Cgmp [5].

Platelets have been implicated as being patho-physiologically important in hypertension and ischemic heart diseases[6]. 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 mutagenic influence (platelet derived growth factor)[7].

Rheological factors also affect the platelet functions in many ways. It has been discovered that rheological factor mediate the binding of von Willebrand Factor (vWF) to platelets *in vivo*[8]. It is mostly dependent on mechanical force i.e. shear stress, which is defined as the force per unit area between lamiae of blood. The platelet receptors complexes which are involved in this reaction are Gp Ib/IX/V are Gp IIb - IIIa. There is an indirect evidence that fibrinogen may be the binding ligand affecting platelet aggregation at the stress below 12 dynes/cm². At stress above 12 dynes/cm^2 platelet secretion and aggregation depend on vWF, platelet Gp Ib/IX/V and Gp IIb- IIIa, is independent of plasma or platelet fibrinogen[9].

When the time averaged mean shear stress level in the arterial circuit reaches pathological level, as in stenosed arteries, it results in thrombus formation. Prostacyclin derived from endothelial cells, inhibits shear-stress induced platelet thrombus formation on subendothelium[8].

Many vessel wall factors also influences the thrombus formation such as vascular endothelium, collagen, insoluble vWF, fibrinogen, thrombospodin, laminin, fibronectin etc. Endothelium produces vaso-relaxing and antiplatelet factor[8] which in healthy conditions are known to increase with exercise[10]. Atherosclerosis and the attending endothelial dysfunction may reduce the capacity of endothelial cells to release these products during exercise, thereby enhancing the platelet activating effect of shear[11].

Moderate and strenuous exercise is known to increase the platelet aggregation[12-13], but even low grade exercise, too transiently enhances the whole blood platelet aggregability in patients with obstructive coronary artery disease (CAD). In contrast, the same degree of exercise does not significantly affect the platelet function in subjects without apparent CAD[14].

The response of platelets to a given amount of physical stress is quite variable. Many factors determine the post exercise aggregation behaviour of platelets e.g. age, hypertension, ischemic heart disease (IHD), smoking and exercise habits etc [15,16].

Patients with mild hypertension demonstrated increased in vivo platelet activity after maximal exercise. Similar results have been noted in patients with IHD. However in healthy individuals the results of many studies conducted to observe the effect of exercise on platelet aggregation have given variable results [17].

In view of the above observations the present study has been planned to observe the response of exercise on platelet aggregation in healthy individuals, patients of CAD and patients of diabetes mellitus type 2 with and without CAD.

STRESS & PLATELET AGGREGATION

Stress

During last few decades the human race is being facing a variety of unnatural and unavoidable stresses. The people are living in a state of increasing stressful condition arising from developments in fields of science and technology, increasing environmental pollution, changed life style, disturbed interpersonal relationship, overcrowding, job responsibility, unbalanced diet, disturbances of natural cycle under which human evolution occurred, and many associated mental and emotional causes.

Dr. Hens Selye[18] has defined stress as the "sum of all the nonspecific changes by function or damage". Stress is a fundamental and physiological response, the primary object of which is to maintain life and re-establish normal state. Every day use of word stress contains two different meanings[19].

(i) It is derived from Latin stringer, to draw tight with its implication of a constraining force, and

(ii) As an aphetic form of distress, means hardship or affliction, as of one who is "pulled asunder"

.

Stress can be of several varieties depending on the kind of stressors like[20]

1. **Physical**: Cooling, overheating, enhanced motor activities, overload on immobilisation, a centrifuge, increased or decreased barometric pressure and ultraviolet or ionizing radiation.
2. **Chemical**: Various toxic, narcotic, hormonal and anticancer agents.
3. **Biological**: Foreign sera, bacteria, transplanted tumours etc.
4. **Emotional Stress**: It plays a major role in human beings.

Emotional stress is a reaction to social changes, threat or uncertainty, and frequently causes an imbalance between individual and the environment. There is no doubt that a relationship exists between personality, stress and disease. Maimonides in his essays on health and youth[21] concluded that "emotional disturbances cause marked changes in the body". Hippocrates in 400 BC stated that "Meditation heals evil thought, sadness and woes". Chronic exposure to emotional stimuli also leads to various biochemical changes in the body which may eventually predispose an individual to a pathological condition[22, 23]. Because both positive and negative events can cause stress, some stress is desirable. However, if stress becomes overwhelming or "dis-stress", body defences may respond with an alarm reaction involving elaboration of hormones. Stressors sends immediate stimuli to brain and it in turn mobilizes all the biochemical mechanisms in the body, this results in increased released of catecholamines and other hormones like, growth hormones, adrenocorticotropin, melanocyte stimulating hormone, prolactin, thyroxin, glucagon, renin, erythropoitin, and gastrin[24]. Stress also results in increased secretion of β- endorphin and β-lipoprotein.

The catecholamines and hormones regulated by CNS play role in the immune suppression and pathogenesis of the disease[24]. Stimulation of cortical-hypothalamic-pituitary axis leads to alteration in immune function either indirectly or directly probably by bidirectional neuronal stimulation of lymphoid tissue[25,26].

Many workers have conducted trials relating stress (physical) to platelet aggregation. Their parameter of physical stress was exercise. Exercise leads to sympathoadrenal activation & increase in circulating epinephrine & norepinephrine. Sympathoadreral activation may stimulate platelets via α_2 adrenoceptor activation because both epinephrine and norepinephrine are non selective α-agonists[27].

Cardiovascular Responses to Exercise

Exercise increased cardiac output & blood pressure, alteration in blood flow, resulting in increased shear forces. Shear forces can stimulate platelet aggregability directly especially during exercise or tachycardia and in presence of epicardial artery stenosis. Shear forces additionally promote platelet aggregation through liberation of large multimers of vWF from vascular endothelium. In 1986 Moake et al.[28] derived information that platelet activation & aggregation depends on the presence of plasma vWF and functional platelet receptor complexes - Gp1b/IX, V and GpIIb/IIIa. There is indirect - evidence that fibrinogen may be the bridging ligand effecting platelet aggregation at low shear stress but at more shear stress platelet secretion and aggregation depends on vWF and platelet GpIb/IX/V and GpIIb/IIIa and are independent of plasma or platelet fibrinogen[29-31]. Plasma vWF levels are known to increase after maximal & prolonged physical activity & this may be shear related.

ATHEROTHROMBOSIS[32]

Atherothrombosis is a result of multiple complex cascades of interaction among the endothelial cells of arterial wall, local hemodynamic environment, blood components notably monocytes, lipoproteins, inflammatory process and their mediators and various healing and reparative process. The role of platelets in thrombosis is central and the subject of various scientific studies all over the world[32].

The process of atherothrombosis starts with chronic endothelial injury caused by many factor such as hyperlipidemia, hypertension, smoking, haemodynamic factors, toxins, viruses, homocysteine, immune reaction and leads to endothelial dysfunction such as increased permeability and increased leucocyte endothelial adhesion. The accumulation of lipoprotein in intima where some of them are oxidised triggers an inflammatory reaction. Monocyte adhesion and emigration into intima and transformation into macrophages occurs under the influence of various chemotactic factors along with smooth muscle emigration from media to intima. The macrophages and smooth muscle engulf lipid and convert into foam cells. Enhanced accumulation of lipid both within cells and extracellularly, collection of inflammatory cells and other factors of inflammation such as smooth muscle proliferation and their fibrous activity leading to accumulation of collagen and proteoglycans constitute fibrous cap.

Rupture of plaque's fibrous cap leads to thrombosis. Physical disruption of atherosclerotic plaque commonly causes arterial thrombosis by allowing blood coagulant factor to contact thrombogenic collagen found in the arterial extracellular matrix and tissue factor produced by macrophage derived foam cells in the lipid core of lesion. In this manner site of plaque rupture forms the nidus of thrombi. When the clot formation overwhelms the endogenous fibinolytic mechanism it may propagate and lead to arterial occlusion. In some cases, the thrombus may lyse or organise into a mural thrombus without occluding the vessel, the subsequent thrombin induced fibrosis and healing causes a fibro- proliferative response that can lead to a more fibrous lesion, one that can produce an eccentric plaque that causes haemodynamically significant stenosis[32].

The Role of Platelets in Atherothrombosis

Platelets, which do not interact with the endothelium of normal vessels, play a central role in atherothrombosis by adhering to exposed subendothelial structure in damaged vessels. Subsequent platelet activation triggers a cycle of recruitment and addition of additional platelets and results in expression and assembly of receptor for fibrinogen on platelet surface. This receptor, the platelet glycoprotein GpIIb/IIIa receptor is the final common pathway for platelet aggregation as its binds to bivalent fibrinogen molecules to form platelet aggregate[33].

Platelets may be activated by several substances; among these ADP plays an important role. ADP is present in high concentration in the dense granules within platelets and can initiate and reinforce aggregation after secretion of these granules. ADP induced platelet aggregation involve three pharmacologically defined human platelet ADP receptors. Activation of these purinoceptors results in change in shape, rise in intracellular calcium, and ultimately, in the assembly of GpIIb/IIIa and expression of P-selectin, a membrane glycoprotein that facilitate interaction between platelets and other cells[33].

Agents that antagonize the platelet aggregating effect of ADP are useful antiplatelet agents. Role of platelets in atherothrombosis is extensively studied as to their behaviour in normal individuals and in patients of ischemic heart disease and diabetes melitus[34]. Results of over 140 trials including more than 73,000 high risk patients shows clearly that antiplatelet drugs reduce the risk of vascular death by about $1/6^{th}$ and risk of nonfatal myocardial infarction (MI), by $1/3^{rd}$ in patients with unstable angina, suspected acute coronary events or a past history of ischemic heart disease[35].

MATERIAL AND METHODS

The present study was conducted on 40 male volunteers between the ages of 40 to 60 years. The study was approved by institutional ethical committee and after informed consent the selected individuals were categorized in four groups of 10 each.

- Group I (n=10) Healthy group. This group included volunteers with no evidence of CAD, Diabetes or any metabolic or endocrinal diseases
- Group II (n=10) CAD group. This group included patients with documented IHD
- Group III (n=10). This group included patients with diabetes mellitus type 2 (DM type 2) but without evidence of IHD
- Group IV (n=10). This group included patients who had both DM type 2 and IHD

All the study participants were subjected to stress test on computerised treadmill so as to complete stage III of Bruce Protocol to be eligible for the study.

The diagnosis of CAD and DM type 2 were based on the criteria given below:

Diagnosis of CAD

1. ECG:

(a) Documentation of old healed myocardial infarction.

(b) ST depression of ≥ 2mm in consecutive leads with or without symptoms[36].

2. ECHO: Regional wall motion abnormalities (RWMA)[37]

3. Positive TMT[38]:

(a) Horizontal or down sloping ST segment depression of ≥ 1mm 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.

DIABETES MELLITUS (DM) TYPE 2[39]

The diagnosis of diabetes mellitus type 2 will be based on the criteria described by ADA. These include -

1. Symptoms of DM plus random blood glucose > 200 mg/dl, or
2. Fasting plasma glucose ≥ 126 mg/dl or
3. Two hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test.

Patients with liver disease, thyroid disease, stroke and those who were on antiplatelet agents or NSAIDS were excluded by history and relevant investigations. Similarly those who used to consume tobacco in any form were also excluded from the study.

STRESS TEST

The stress test was done by asking the volunteer to complete stage III of the Bruce protocol.

Bruce multistage maximal treadmill protocol has 3 minute

periods to allow achievement of a steady state before work load in increased. The speed of the treadmill is as follows-

Stage	Speed
Stage I	2.8 km/hr
Stage II	4.2 km/hr
Stage III	5.7 km/hr

Stage I has an elevation grade of 10 percent, increasing by 2 percent for every stage.

TECHNIQUE[38]

1. Patient should be instructed not to eat, drink caffeinated beverages or smoke for 3 hours before testing.
2. A brief history and physical examination should be performed; the risks and benefits of the procedure should be explained.
3. A 12 lead ECG should be obtained with the electrodes on the distal extremities.
4. After the standard 12 lead ECG is recorded, a torso ECG should be obtained in the supine position and in the sitting or standing position. The ECG and blood pressure should be recorded in both position and patients should be instructed on how to perform the test.
5. Prior to electrode application, the area of electrode application are rubbed with an alcohol saturated pad to remove oil and rubbed with rough material to reduce skin resistance to 5000 ohms or less.
6. Room temperature should be between 64 and 72°F (18 and 22°C) and humidity less than 60 percent.
7. The heart rate, blood pressure and ECG should be recorded at the end of each stage of exercise, immediately before and immediately after stopping exercise, at the onset of an ischemic response, and for each minute for at least 5 to 10 minutes in the recovery phase.
8. A minimum of three leads should be displayed continuously on the monitor during the test.

Study Protocol

After an overnight fast, venous blood sample (4 ml) was collected without undue pressure from the selected patient. The patient after brief history, physical examination & written consent was subjected to the stress test. Another sample (4 ml) was collected at the end of completion of stage III of Bruce Protocol on the TMT. Both the blood samples were subjected for estimation of platelet aggregation on ELVI-840 Aggregometer and Omniscribe chart recorder[40].

PLATELET AGGREGATION

Platelet-rich plasma (PRP) was prepared by centrifugation of anticoagulant sample at 250 × g for 10 minutes at room temperature. Aliquots of PRP (450 µL) were placed in disposable polystyrene cuvettes. Platelet-poor plasma (PPP) was obtained by re-cenrtification of the original blood sample at 1,500 × g for 10 minutes. Platelet aggregation was measured turbidimetrically better termed as light transmittance aggregometry (LTA) on ELVI-840 aggregometer and Omniscribe chart recorder. The measurement of aggregation was performed exactly after 30 minutes of sample collection to avoid differences of the aggregation due to altered status of the platelet resulting from ex-vivo conditions. After 10 minutes of equilibrium at 37°C and constant stirring at 1,000 rpm, the aggregation of PRP was induced by ADP (6 µmol/L) or collagen (0.2 µg/mL) (Sigma), the response was recorded for 5 minutes, and the results were expressed as percentage aggregation[40].

Expected Values:

ADP = 80-100%

Epinephrine = 67 - 97% (subjects with secondary aggregation phase)

= 26-59% (Subject without secondary aggregation phase)

Collagen = 80 -100%

Performance Characteristics:

Duplicate aggregation determination on platelet rich plasma (PRP) from normal individual yielded an average difference of ±3% aggregation for collagen, ADP and epinephrine aggregation determination.

Statistical Analysis[41]

All data are expressed as mean $\pm$ SE. The results were analyzed with Student's t test for paired data. A p value of <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The effect of stress (TMT) on platelet aggregation in normal individuals showed that there was a significant ($p<0.05$) decrease in platelet aggregation after stress induced by ADP and collagen [Table 1, Figure 1]. ADP induced platelet aggregation decreased from a mean of 52.75 ± 9.84 to 42.38 14.20 percent. This decrease is around 20 percent which is significant ($p<0.05$). Similarly collagen induced platelet aggregation also decreased from a mean of 52.25±8.23 to 40.25±15.10 percent, which is around 21 percent and statistically significant ($p<0.05$).

Table 1: Effect of Stress (TMT) on Platelet Aggregation (Percent) in Healthy Individuals

S. No.	ADP		COLLAGEN	
	Pre TMT	Post TMT	Pre TMT	Post TMT
Mean	52.75	42.38	51.25	40.25
SD ±	9.84	14.20	8.23	15.10
SE ±	3.11	4.49	2.60	4.78
% Change		-19.67		-21.46
p Value		$p < 0.05$		$p < 0.05$

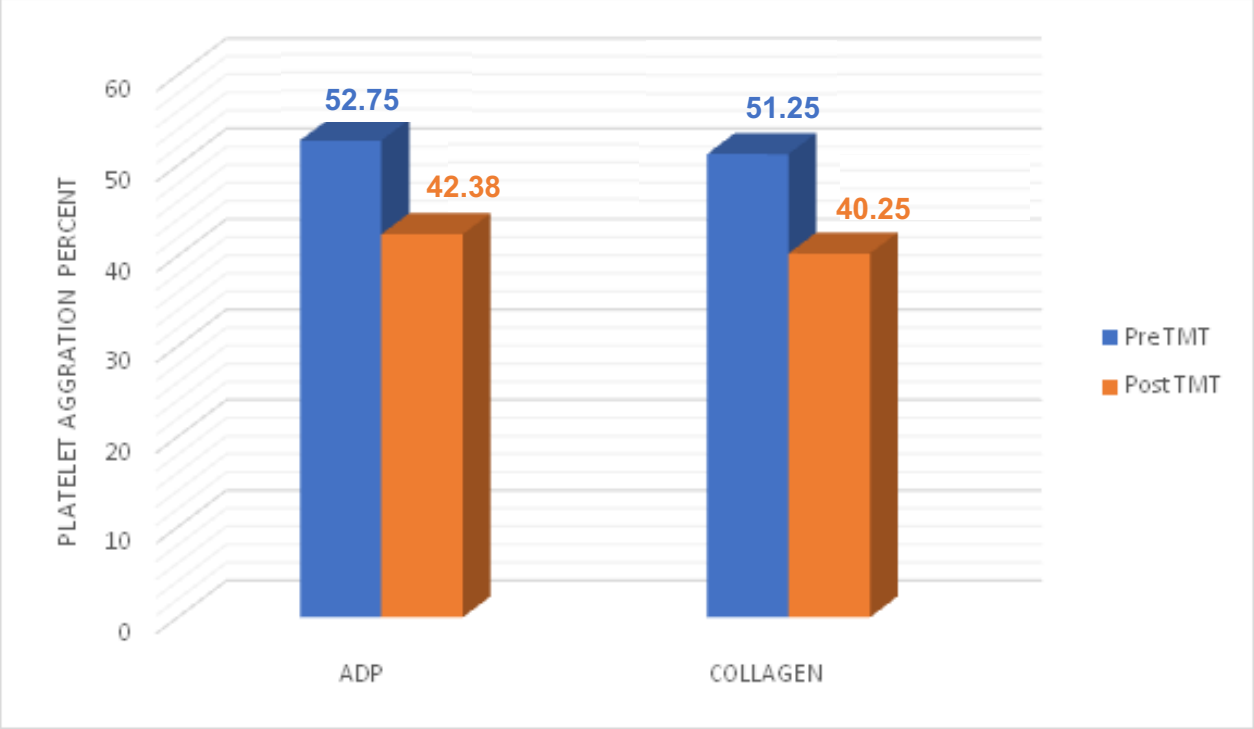

Figure 1: Effect of stress (TMT) on platelet aggregation (percent) in healthy individuals

The effect of stress (TMT) on platelet aggregation in patients of Ischemic Heart Disease (IHD) has been shown in Table 2. There is an increase in ADP induced platelet aggregation after stress from a mean of 46.38±13.48 to 59.75±13.89 percent. This increase is around 29 percent which is statistically significant ($p<0.001$). Similarly there is also an increase in collagen induced platelet aggregation after exercise, from a mean of 39.70±11.24 to 57.63±9.97 percent. This increase is around 45.15 percent and also statistically significant ($p<0.01$) [Figure 2].

Table 2: Effect of Stress (TMT) on Platelet Aggregation (Percent) in Patients with IHD

S. No.	ADP		COLLAGEN	
	Pre TMT	Post TMT	Pre TMT	Post TMT
Mean	46.38	59.75	39.70	57.63
SD ±	13.48	13.89	11.24	9.97
SE ±	4.26	4.39	3.55	3.15
% Change		28.84		45.15
p Value		p < 0.001		p < 0.01

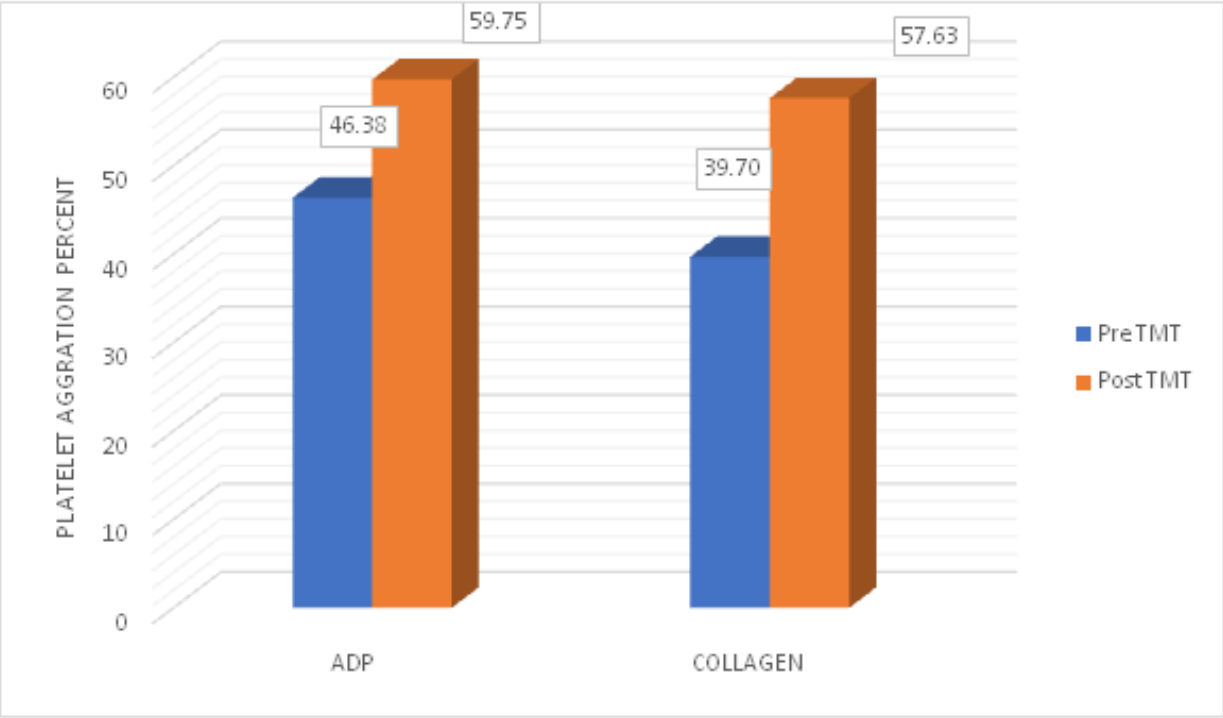

Figure 2: Effect of stress (TMT) on platelet aggregation (percent) in patients with ischemic heart disease

The effect of stress (TMT) on platelet aggregation in patients with type 2 diabetes mellitus was unremarkable (Table 3). There is a decrease in platelet aggregation, induced by ADP after exercise from a mean of 51.38±14.74 to 50.58±16.15 percent. This decrease is around 2 percent and is not statistically significant (P = NS). In the same patient there was an increase of platelet aggregation induced by collagen from a mean of 47.83±13.47 to 48.33±14.43 percent. This increase however is statistically not significant (P = NS) [Figure 3].

Table 3: Effect of Stress (TMT) on Platelet Aggregation (Percent) in Patients with Type 2 Diabetes

S. No.	ADP		COLLAGEN	
	Pre TMT	Post TMT	Pre TMT	Post TMT
Mean	51.38	50.58	47.83	48.33
SD ±	14.74	16.15	13.47	14.43
SE ±	4.66	5.11	4.26	4.45
% Change		-1.56		1.05
p Value		NS		NS

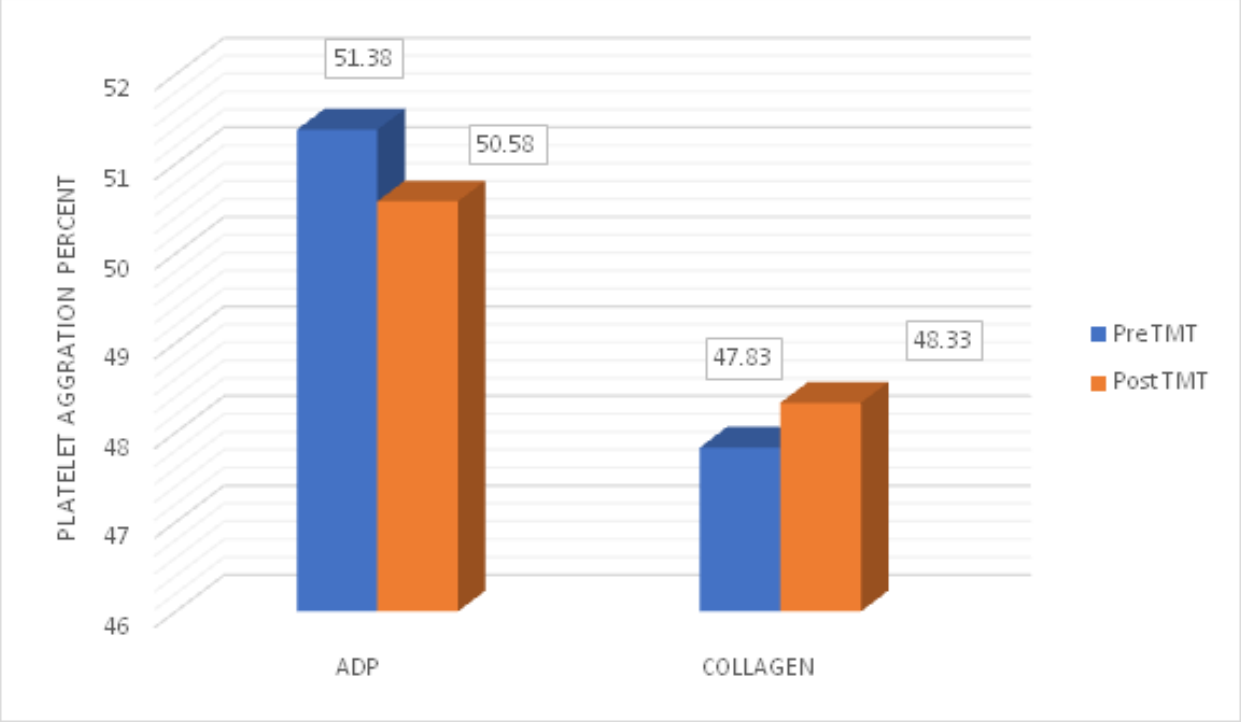

Figure 3: Effect of stress (TMT) on platelet aggregation (percent) in patients with type 2 diabetes

Table 4 shows the effect of stress (TMT) on platelet aggregation in patients with type 2 diabetes and ischemic heart disease. The platelet aggregation as induced by ADP showed an increase from a mean value of 56.75±7.60 to 61.75±8.76 percent which is an increase of 9 percent and is statistically significant ($p<0.05$). Similarly the platelet aggregation induced by collagen also showed an increase from a mean of 53.60±8.73 to 59.63±8.06 percent which is around 11 percent and is also statistically significant ($p<0.05$) [Figure 4].

Table 4: of Stress (TMT) on Platelet Aggregation (Percent) in Patients with Type 2 Diabetics and IHD

S. No.	ADP		COLLAGEN	
	Pre TMT	Post TMT	Pre TMT	Post TMT
Mean	56.75	61.75	53.60	59.63
SD ±	7.60	8.76	8.73	8.06
SE ±	2.40	2.77	2.76	2.55
% Change		8.81		11.24
p Value		p < 0.05		p < 0.05

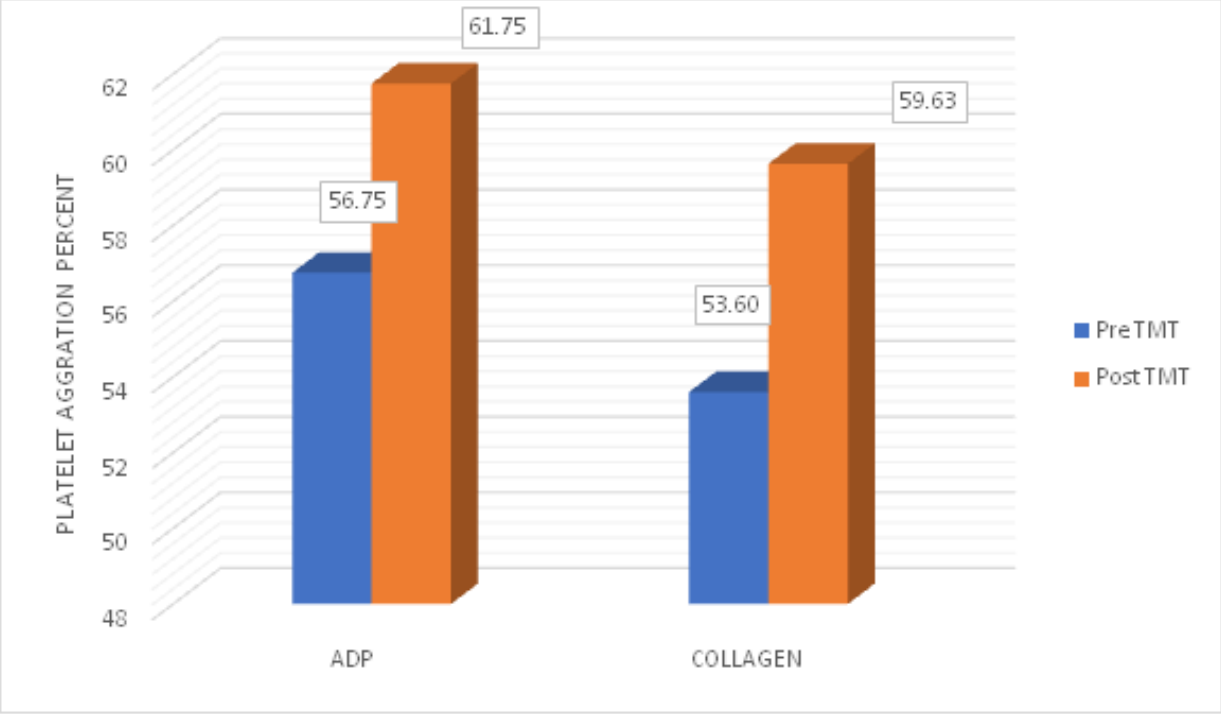

Figure 4: Effect of stress (TMT) on platelet aggregation (percent) in patients with type 2 diabetes and ischemic heart disease

DISCUSSION

The present study was designed with the aim to observe the effect of stress (TMT) on platelet aggregation in normal individuals, persons with type 2 diabetes mellitus, patients with ischemic heart disease and patients who had type 2 DM with ischemic heart disease.

The study was conducted on 40 male volunteers between the age of 40 to 60 years and were categorized in four groups of 10 each.

Group I constituted of healthy individuals

Group II had established patients of coronary artery disease.

Group III was of type 2 diabetes mellitus

Group IV had both coronary artery disease and diabetes mellitus type 2

In the present study of stress (TMT) on normal individuals, ADP induced platelet aggregation was decreased around 20 percent, which is statistically significant ($p<0.05$). The collagen induced platelet aggregation also decreased significantly ($p<0.05$). [Table.1, Figure 1]

In the case of patients with ischemic heart disease (IHD) stress (TMT) increased platelet aggregation induced by ADP by about 29 percent induced by ADP which is also statistically significant ($p<0.05$) (Table 2). The collagen induced aggregation also showed an increase of around 45 percent, which is also significant statistically ($p<0.01$) [Figure 2].

In the case of patients with type 2 diabetes mellitus, the ADP induced aggregation showed a marginal decrease of around 2 percent which is statistically not significant (P=NS). Similarly the collagen induced aggregation showed a marginal increase of around 1 percent which was not significant statistically (P=NS). [Table 3, Figure 3]

Patients who had both IHD & type 2 DM, the ADP induced aggregation increased after exercise from a pre TMT mean of 56.75±7.60 percent to post TMT mean of 61.75±8.76 percent which was 9 percent and was significant statistically ($p<0.05$). Similarly the collagen induced aggregation showed an increase of around 11 percent with a mean change from 53.60±8.73 to 59.63±8.06 and was statistically significant ($p<0.05$). [Table 4, Figure 4].

Many studies have reported that the response of platelet aggregation in healthy individuals is quite variable. In a study maximal exercise lowered platelet activity in young volunteers[42]. Other studies on the effect of exercise on platelet aggregation have given variable results[15-17]. Some of the inconsistency surrounding the effect of exercise on platelet aggregation can perhaps be explained by differences in physical condition: healthy young individuals who do not engage in regular exercise, platelets show increase in aggregability during exercise, whereas those already participating in an exercise[43,44]. programme show the opposite" Similarly, the failure of exercise to reduce platelet aggregability in elderly people could be explained by their generally low level of physical activity. Another factor could be that young people release more platelet inhibitors (prostacyclins and nitric oxide) from the vessel wall than do the elderly, who have a feebler functional capacity of the vascular endothelium as a result of atherosclerosis. In our study it was found that there is a decrease of platelet aggregation, which suggests a healthy endothelium with normal release of platelet inhibitors.

In studies in patients of IHD, exercise showed an increase in platelet aggregation which was substantiated by our study which demonstrated a very significant increase ($p<0.001$) for ADP and collagen ($p<0.05$). This shows that stress is harmful and may precipitate cardiovascular events. It is likely that other forms of stress have similar effect as that of exercise (TMT), and therefore stress in any form should be avoided in patients of IHD. Plasma platelet factor 4 (PF - 4) (a heparin neutralizing protein) is found to increase in IHD during exercise and may account for the increase in platelet aggregation[45].

Studies Related with Stress Induced Platelet Aggregation

Tanigaiva and Colleagues[46] conducted a study in which 36 patients of Acute Myocardial infarction (AMI) who were successfully treated with primary angioplasty were randomised to 3 antiplatelet regimens.

The diagnosis of MI was documented by the characteristic history of prolonged chest pain, diagnostic ECG change & elevation of cardiac enzymes. Stable CAD was defined as either stable angina or previous MI. 12 patients with stable CAD who had angiographically documented CAD, who were not receiving Acetyl Salicylic Acid (ASA) or other agents known to alter the platelet function during 2 weeks, were included for comparison. No subject with stable CAD has pain at rest or a MI within 3 months before the study. 36 patients with AMI were taken who were given a bolus injection of 5,000 IU of unfractionated heparin and 81 mg. of ASA. All patients were randomly assigned to 1-3 treatment groups each including 12 patients.

(i) ASA group - 81mg

(ii) ASA (81 mg/day) + Ticlopidine (200 mg/day)

(iii) ASA (81 mg/day) + Cilostazol (200 mg/day)

Before angioplasty 5000 IU heparin was administered intra arterially. Patient received IV heparin for 24 hours. Blood samples were taken 1 day before antithrombotic therapy and on 7th day of antithrombotic therapy.

Platelet aggregability, vWF activity were checked. There were no significant differences in platelet aggregation induced by epinephrin & arachidonate among normal subjects and pts with AMI & stable angina. The extent of ADP induced aggregation was significantly high in patients with AMI, in comparison with normal controls. The extent of collagen induced aggregation was also significantly increased in AMI patients

compared with stable patients. The extent of stress induced platelet aggregation (SIPA) in patient with AMI was significantly higher than that in patients with stable CAD or normal patients. However, the extent of SIPA in patients group were similar to that in age matched normal control group. Plasma vWF was significantly higher in patients with AMI than in patients with stable CAD. There was a significant correlation between SIPA and ADP induced platelet aggregation. Inhibition of SIPA by ASA and Cilostazol in AMI group is found after coronary angioplasty. Platelet aggregation in response to collagen and arachidonate was significantly inhibited by low dose ASA alone in patients with AMI who underwent coronary angioplasty.

ADP induced platelet aggregation was inhibited by ASA + ticlopidine, SIPA was inhibited by ASA & ticlopidine as well as by ASA & cilostazol but not by ASA alone. Administration of Antiplatelet drugs did not affect plasma von Willebrand factor activity[46].

The present finding of increased aggregation in response to ADP or Collagen agrees with observation by other investigators studying CAD[47,48].The difference in SIPA between patients with AMI & patients with stable CAD may reflect difference in the pathogenesis of underlying condition. AMI most often results from coronary plaque disruption with consequent platelet aggregation and thrombosis resulting in a critical decrease in coronary blood flow[49]. von Willebrand factor is established to be a key molecule involved in acute occlusion of atherosclerotic Vessel. The present study indicates that SIPA significantly correlates with platelet aggregation induced by ADP among the agonists tested. This is consistent with the finding that ADP is an essential cofactor for SIPA mediated by large vWF multimer, because SIPA is inhibited by ADP removing enzymes.These data suggest that pharmacological modification of SIPA might be clinically important in decreased the risk of coronary thrombosis in patients with CAD. SIPA was unchanged by 81 mg/day ASA therapy is patients with AMI. Although this alone was sufficient to suppress platelet aggregation induced by arachidonate & collagen. Only the combination with ASA+Ticlopidine significantly inhibited ADP induced platelet aggregation. Thus collectively combination therapy with ASA+Cilostazol may be effective not only in preventing sub acute thrombosis but also in decreasing rate of restenosis after balloon angioplasty or stent implantation[46].

Moderate and strenuous exercise is known to increase the platelet aggregation but even low grade exercise too, transiently enhances the whole blood platelet aggregability in patients with obstructive coronary artery disease. In contrast the same degree of exercise does not significantly alter the platelet function in subjects without apparent CAD[50].

Low grade exercise induced platelet aggregation was studied in 27 patients with documented CAD who were receiving aspirin and 12 subjects without CAD. All the subjects refrained from their usual medication for 24 hours before the study and from caffeine on the day of test. All were subjected to low grade tread mill test (≤ stage III of multi stage modified Bruce protocol). Venous sample was drawn at baseline, immediately after exercise & at 30 & 180 min. after test. The results showed that with exercise, both groups of patients with CAD (with and without exercise induced ischemia) showed a significant reduction in aggregation at peak compared with base line whereas no significant change occurred in control. vWF were similar in all three group & did not change with exercise. At peak exercise there was a significant increase in hematocrit in both CAD group but not in control. Platelet count showed a significant increase at peak exercise only in group I. WBC ↑ significantly at peak in all 3 groups.

The novel finding of this study is that even low grades of exertion transiently enhance whole blood platelet aggregability in patients with obstructive CAD. These findings suggest that platelet aggregability in enhanced by exercise in the presence of coronary atherosclerosis per se, as a result of hemodynamic factors interacting with arterial obstruction or more generally with endothelial dysfunction[64]. Vascular endothelium produces vaso relaxing & antiplatelet factor which is healthy conditions are known to increase with exercise. Atherosclerosis and the attending endothelial dysfunction may reduce the capacity of endothelial cells to release these products during exercise thereby enhancing the platelet activating effects of shear[51,52].

In this study vWF level did not display significant changes with exercise, possibly due to the low degree of exertion or to the failure to discriminate between the smaller and larger multimers of vWF[53].

In a study conducted by Green and co-workers it was found that patients with coronary artery disease (CAD) who underwent exercise stress test had elevated levels of platelet factor 4 (PF-4) a heparin neutralizing protein that is specifically released from platelets at the time of aggregation. 40 patients had blood samples withdrawn for measurement of the plasma level of PF-4 before and after a standardized exercise tolerance test. 20 patients had positive exercise tests and 19 of these 20 had clinical or angiographic evidence of CAD. Eleven of the 20 had a greater than 50 percent increase in PF-4 after exercise. The remaining 9 had positive exercise tests without rise in PF-4. Elevated level returned to normal within 15 minutes of exercise. 18 of the 20 patients with negative exercise tests had no use of PF-4 after exercise.

In the patients who had positive exercise tests, there was a major difference between those with normal PF-4 levels and those with increased PF-4 levels. Only 2 of the 9 patients with normal PF-4 levels (25 percent) had chest pain during exercise test. The remaining 7 had marked ST segment depression without concomitant pain. In contrast 10 of the 11 patients (91 percent) who had increased PF-4 levels during exercise had their exercise tests limited because of typical angina pectoris. Thus it was concluded that patients with CAD and exercise induced myocardial ischemic had evidence of platelet activation and secretion[23].

In a study conducted by Gberup and co-workers, maximal exercise lowered platelet activity in young volunteers. Previous studies of the effect of exercise on platelet aggregation had given variable results. Some of the inconsistency surrounding the effect of exercise on platelet aggregation can be explained by the differences in physical condition: healthy young individual who did not engage in regular exercise increased their aggregability during exercise, whereas those already participating in an exercise programme did the opposite[43,44].

In another study increase circulating catecholamines with exercise can stimulate the pro aggregatory α_2 adrenoreceptor on platelet membrane but in this study no significant change in platelet aggregability occurred at peak exercise in control group, despite similar or significantly higher rate - pressure products compared with the CAD group. Thus this study suggests that even mild exertion increases shear rates at sites of critically stenotic arteries. This together with impaired secretion of anti-platelet agents by atherosclerotic vessels in likely responsible for the hyperactive platelet response after mild physical activity[54].

Platelets can associate with one another by aggregation or agglutination[55]. Aggregation requires platelet activation to engage the platelet integrin α IIb β3 and in generally irreversible whereas agglutination is mediated by mechanical cross linking that is likely reversible vWF mediate both platelet aggregation and agglutination and is required for shear induced platelet association. Previous studies showed that shear induced platelet aggregation required α-granule release but in this study it was found that majority of the sheared platelet had not secreted α- granules. These results suggest that the majority of sheared platelet may not be activated and aggregated, but rather agglutinated by mechanical cross linking.

Although exact mechanism of this cross linking is unclear but one can speculate that vWF may be modified by shear in such way that it could interact with platelet in the absence of modulator. This is different from platelet adhesion to sub endothelium which is receptor mediated and requires platelet activation. The finding may be physiologically significant through an in vivo protective mechanism whereby platelets subjected to a brief high fluid shear stress may first agglutinate reversibly. These reversible & unstable agglutinates may rapidly disaggregate to prevent formation of irreversible aggregation & therefore thrombus formation[56].

Likely mechanisms that lead to increased platelet aggregability in patients of CAD as compared with those without CAD are:

1. Atherosclerosis and the attending endothelial dysfunction may reduce the capacity of endothelial cells to release vaso-relaxing and antiplatelet factors[54,57]
2. Shear forces can stimulate platelet aggregability directly esp. during exercise, as well as by release of vWF from vascular endothelium[58-60]
3. Increased circulating catecholamines with exercise can stimulate that pro-aggregatory α_2 - adrenoreceptors on platelet membranes[27]
4. Increased level of platelet factor four (PF-4) after exercise inpatients of CAD reflecting increased platelet aggregability[61,62]

It has also been found that vascular endothelium produces vaso-relaxing and antiplatelet factors conditions are[63,64] which in healthy known to increase with exercise[65,66]. Atherosclerosis and the attending endothelial dysfunction may reduce the capacity of the endothelial cells to release these products during exercise[68,52,67] hereby enhancing the platelet activating effects of shear.

Patients with diabetes mellitus did not show any significant change in platelet aggregation but those having both IHD and Diabetes Mellitus showed a significant increase in platelet aggregation induced by ADP and collagen most likely due to the effect of IHD and diabetes on the vascular endothelium.

CONCLUSION

The study therefore concludes that-

(1) The physical stress (TMT) in healthy individuals reduced platelet aggregation induced by both ADP and collagen, highlighting that regular exercise helps prevent platelet aggregation.

(2) The effect of stress (TMT) in patients with IHD showed a statistically significant ($p<0.01$) increase in platelet aggregation induced by both ADP and collagen.

(3) The effect of stress (TMT) in patients of Diabetes Mellitus did not show any statistical significant change in platelet aggregation induced by any aggregating agent.

(4) The effect of stress (TMT) in patients having both IHD and Diabetes Mellitus showed a statistically significant ($p<0.05$) increase in platelet aggregation induced by ADP and collagen.

In view of the above factors the importance of regular exercise cannot be overemphasized. Past studies have documented that in patients with coronary artery disease physical exercise induced platelet aggregation may not be checked by regular administration of common anti platelet agent - aspirin. This fact needs further attention in management of patients with IHD in order to offer better therapeutic options.

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Pictorial CME

Diaphallus - A Rare Anomaly of the Penis

A male child was brought to surgical OPD for the abnormality of the penis. The child had two penises. During examination the child urinated and the urine came out in two streams from two urethras [Figure 1].The penile duplication is an extremely rare disorder with only approximately 1000 cases of diphallia recorded since the first case reported by Jahannes Jacob Wecker in 1609[1]. This occurs when the baby is born with 2 penises and it is seen in 1 out of 5,000,000 male births.

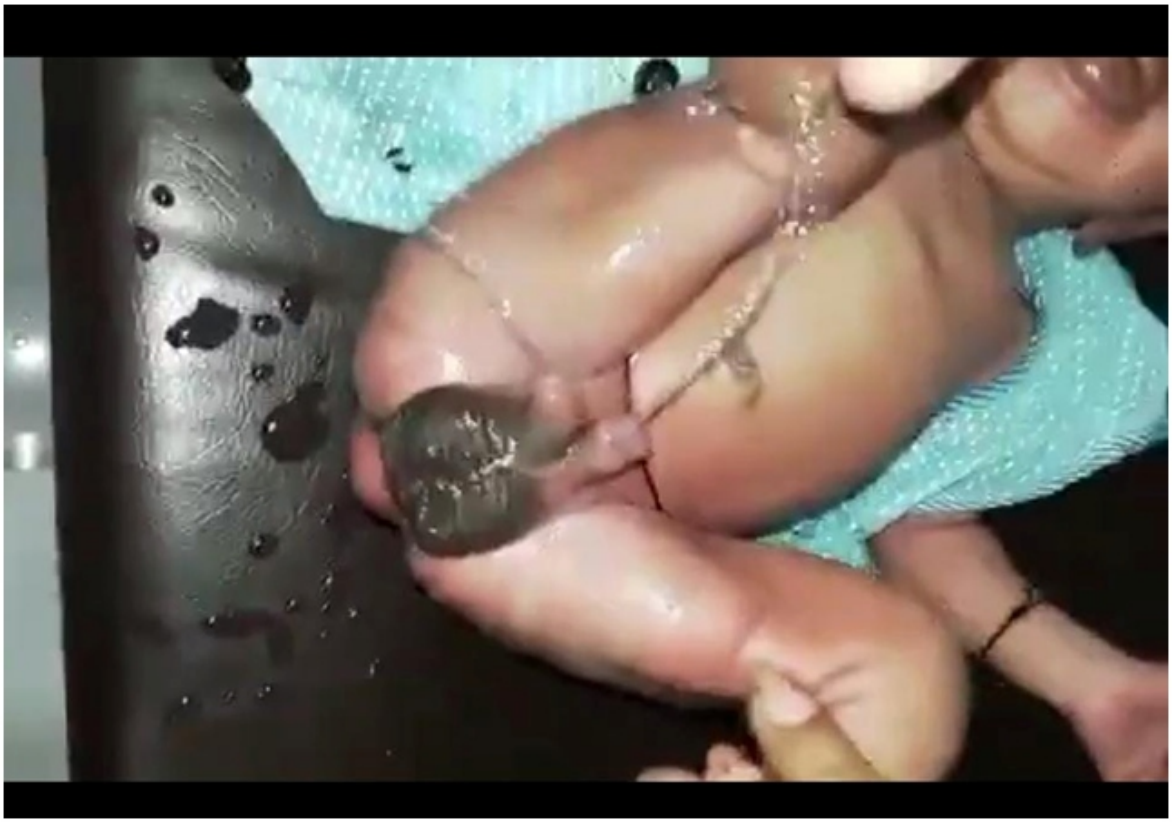

Figure 1: Double penises, two urine streams through two separate urethras

Generally, a child that is born with penile duplication will also have other congenital defects, including spina bifida. Babies born with this condition are at an increased risk of infant death because of the defects and infections that are associated with it. Penile duplication develops around 23–25 days of gestation because the genital tubercle fails to fuse properly[2]. Treatment should always be individualized. The malformations that are potentially life-threatening should be solved first[3]. Intestinal anomalies are frequently associated with complete diphallia and imperforate anus[4].

Embryologically a diphallus deformity arises from either "separation" of the pubic tubercle, wherein each phallus will have only one corporal body and urethra, or "cleavage" of the pubic tubercle wherein each phallus will have two corporal cavernous bodies and urethras[5].

Diphallus has been classified in different ways, such as glandular, bifid, concealed, and complete, hemidiphallus and triple penis[6]. Schneider classified diphallus in three groups: diphallia of glans alone, bifid diphallus, and complete diphallia[6]. Vilanova and Raventos have added a fourth category called pseudodiphllia[7]. The majority have a single corpus cavernosum in each organ[8].

DISCUSSION

Duplication of the penis or diphallus is a rare anomaly. Diphallus may happen in clitoris which is also very rare, as reported by Jeffcoate[9]. Scheneider classified diphallus in three groups: diphallus of glans alone, bifid diphallus, and complete diphallus.

The meatus may be normal, hypospadiac[6], or epispadiac. The scrotum may be normal or bifid. Priyadarshi has reported a case of bifid scrotum[8]. Associated congenital anomalies are present in the majority of cases. Bifid scrotum, hypospadias, duplicated bladder, imperforate anus, bladder exstrophy, colon duplication, inguinal hernia and kidney agenesis have been reported in different studies[10,11,12].

Intestinal anomalies are mostly associated with complete diphallia, and imperforate anus[8,13]. There are multiple embryological explanations for diphallus.

Treatment of diphallus usually includes excision of the duplicated penile structure and its urethra. Associated anomalies can also be repaired surgically[1,13,14].

In short all the patients with penile duplication (diphallus) have to be evaluated carefully because of the high incidence of other systemic anomalies and all can be repaired surgically.

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Review

Mean Platelet Volume in Different Clinical Conditions with Special Reference to Diabetes and its Complications – A Short Review

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ABSTRACT

Platelets play a major role in integrity of normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function .The large platelets contain more dense granules are more potent than smaller platelets and hence more thrombogenic . Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelet. Increase in MPV has been documented in patients with metabolic syndrome, stroke and diabetes mellitus (DM). Many studies have shown that increased MPV is one of the risk factors for myocardial infarction, cerebral ischemia and transient ischemic attacks. On the contrary, MPV is decreased in bone marrow failure. Both the situations are critical because high MPV can lead to blood clot formation and a low MPV may lead to bleeding or bruising. MPV, therefore, can be used as an important, effortless, simple and cost – effective tool for assessing functions of platelets and for predicting risk of cardiovascular diseases and the possibility of impending micro-vascular complications in diabetes mellitus.

KEYWORDS: Cardiovascular diseases, Mean platelet volume, Atherosclerosis, Diabetic complications, Metabolic syndrome

INTRODUCTION

Platelets play a major role in normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function[1] .The large platelets contain more dense granules are more potent than smaller platelets and hence more thrombogenic[1]. Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelet[2,3]. MPV is regarded as a marker for thrombosis, atherosclerosis, and inflammation in various vascular diseases. Not only this, a recent study has focused that MPV level is independently associated with cerebral white matter hyper intensities in non-stroke individuals[4].

Increase in MPV has been documented in patients with metabolic syndrome, stroke and diabetes mellitus (DM)[5]. Altered platelet morphology and function have been reported in patients with DM, and MPV was found to be significantly higher in diabetic patients[6,7]. Many studies

have shown that increased MPV is one of the risk factors for myocardial infarction, cerebral ischemia and transient ischemic attacks[8-12.]

Larger platelets are haemostatically more active and are a risk factor for developing coronary thrombosis, leading to myocardial infarction. Elevated MPV is associated with a worse outcome for acute ischemic cerebrovascular events independent of other clinical parameters[13].

Mean platelet volume is a marker of platelet size which increases in type-2 diabetes mellitus. By altering the platelet morphology and its activity by increasing production of prothrombotic factors such as thromboxane A2, which play an independent risk factor for atherothrombosis, MPV play a significant role in microvascular complications of diabetic patients[5]. It has also been observed that there is a strong association between a low vitamin D level and a high MPV[14].

PLATELETS

Platelets are small nucleate cells that play a critical role in haemostasis and Thrombosis[15]. Platelets were described by Addison in 1841 as extremely minute granules in clotting blood. They were termed platelets by Bizzozero, who observed their adhesive qualities as increased stickiness when a vascular wall is damaged. Platelets play a major role in integrity of normal haematopoiesis, and mean platelet volume (MPV) is an indicator for its function. The large platelets contain more dense granules and are more potent than smaller platelets and hence more thrombogenic[1].

MEAN PLATELET VOLUME (MPV)

Measurement of peripheral blood platelet counts tells little about platelet related haemostatic function unless the platelet count is particularly low. However, most hematology analyzers measure another platelet parameter, the mean platelet volume which can give useful clinical and patho-physiological information about patients and vascular diseases. +MPV is a new and independent risk factor for atherothrombosis. Studies have shown that increased MPV is a risk factor for myocardial infarction, cerebral ischemia, and transient ischemic attacks events. Also recent studies have documented a significant increase in platelet–leukocyte aggregates in diabetics[16].

PHYSIOLOGY OF PLATELET SIZE

MPV appears to be a marker, or even a determinant, of platelet function. Large platelets are more reactive than small platelets in vitro. They preferentially and more rapidly aggregate to platelet agonist including ADP, collagen and adrenaline produce more prothrombotic and vasoactive factors including arachidonic acid metabolites (e.g. ThromboxaneA2), serotonin, β- thromboglobulin and ATP, contains more dense granules, and have higher LDH activity[16]. MPV correlates with platelet aggregation, whether measured in platelet rich plasma or whole blood, populations of subjects or in some disease states, e.g., Diabetes mellitus. Large platelets also express increased levels of adhesion molecules like P-selectin, GPIIb/IIIa, although the surface density of these glycoproteins is usually constant, independent of platelet volume[16].

MEASUREMENT OF PLATELET VOLUME

The optimal method for measuring platelet volume utilises changes in either electrical impedance (as used in Coulter haematology analysers) or light diffraction (as used by Technicon) when a platelet passes through an arrow aperture. Alternative and less satisfactory methods include semi-quantitative measurement of diameter on platelet smears, or using flow cytometry[16].

In the Coulter series, cell shield in fluid suspension are flown through a small aperture, thereby creating a change in voltage proportional to particle size. A raw histogram is generated, and a log-normal curve is fitted to the data. Platelet count is derived from this together with the MPV, which is calculated by numerical integration. Similarly, the Sysmex measures parameters with cells in fluid suspension, although in addition the cells are hydro-dynamically focused, ensuring that cells travel in a straight line through the aperture. This prevents cells flowing through attached of the aperture and causing spurious changes in the electrical field. It also differs from Coulter in that the upper and lower discriminators are both mobile[12].

In contrast, Technic on instruments uses laser-optic technology to measure the size and granularity of cells in suspension. A beam of light is passed through cells, and the amount of forward scatter is proportional to size of particles, whereas side scatter equates to density or granularity. A platelet histogram is derived from the data, and MPV is calculated as the mode. Differences of up to 40% have been found when Coulter and Technicon results have been compared[12].

Complete blood count specimens are usually ant coagulated in EDTA which causes platelet to swell in a time dependent manner. Most of the increase in MPV occurs during the first 1.5 hr but the process continues over the next 24 hrs. EDTA is thought to increase intracellular cyclic AMP and change plasma membrane permeability[12]. This situation is further complicated since analysers utilising light diffraction measure particle size by assessing optical density. These analysers record decreasing MPV with times in platelet swelling results in a lower optical density. As a result, studies reporting raw MPV measurements made in EDTA are of questionable clinical or research value unless MPV is assessed data consistent time following phlebotomy, or once the swelling has ceased at 24 hrs. In contrast MPV measured in high concentration sodium citrate does not change with time and hence is considered as the gold standard[16].

NORMAL VALUES FOR MPV[16]

The normal range for mean platelet volume has yet to be adequately determined, but studies show that MPV in normal subjects ranges from 7 – 11.7 fl. The day to day variation in MPV is small (CV=2.1%) compared with platelet count. (CV = 6.1%). Both the size and number of granules in platelets in circulation are under independent hormonal control and do not change during the life span of the platelets[2,3].

ALTERATIONS IN MPV[17]

High MPV may be due to cancer, cardiac disease etc. and low PMV may mean that the bone marrow is not functioning well and not producing enough new platelets; therefore, most of the platelets are old.

Causes of High MPV

- Cancer
- Massive hemorrhage
- Hyperthyroidism
- Diabetes
- Vitamin D deficiency
- Heart disease
- Hypertension

Causes of Low MPV

- Aplastic anemia
- Lupus
- Chemotherapy
- Hypothyroidism
- Iron deficiency anemia
- HIV/AIDS
- Autoimmune diseases
- Alcohol use disorders
- Genetic conditions

Cancer with high MPV – Gastric, Breast, Endometrium, Thyroid and Lung cancer.

Cancer with low MPV – Renal cell carcinoma, Gall bladder cancer.

Implication of altered MPV [17]

High MPV can lead to increased tendency of blood clotting. It is because of larger platelets which are more active. Increase in blood clotting poses a risk of stroke and deep vein thrombosis. Low MPV, on the other hand, brings the situation of more bruising and/or bleeding. The reason behind the bruising is that older platelets, which are smaller, may not work properly.

MPV AND AGE

It used to be thought that the platelet size decreased with age, but more recent evidence suggests that MPV and other platelet parameters and therefore platelet protein content and reactivity, are determined primarily at or before thrombopoesis by the platelet precursor cell, the MK[30]. Khalid et al.[31] concluded that Increased MPV was found in a significant number of patients and was more in the males and patients with age greater than 50 years[18].

MPV AND GENDER

Gender dependent differences in platelet count have been demonstrated in few studies. Butkiewiczetal[32] conducted a study on healthy blood donors divided into groups: 60 women and 65 men. No statistically significant differences were found in the mean platelet volume, though there was a slight increase in females[19].

MPV AND HYPERTENSION

Coban et al. selected 36 essential hypertensive patients, 36 white coat hypertensive subjects and 36 normotensive control subjects matched for age, gender, and body mass index. MPV was very significantly higher in essential hypertensives and white coat hypertensives than in normotensives (P & lt; 0.00); it was also higher in essential hypertensives than in white coat hypertensives (P & lt; 0.05). MPV was positively correlated with ambulatory diastolic blood pressure in essential hypertension and white coat hypertension groups (P & lt; 0.05)[20].

MPV AND METABOLIC SYNDROME

Giuseppe Lippi et al. performed a retrospective analysis. Cumulative results for MPV, FPG, HDL and triglycerides were retrieved for 3337 outpatients & gt; 35 years of age over the 2 year period. The mean MPV of subjects with all biochemical markers suggestive of the metabolic syndrome was slightly higher but not significantly different from that of control subjects, i.e., 8.7 fL (95% CI 7.7, 9.6) versus 8.6 fL (95% CI 7.5, 9.6), respectively (p= 0.119)[21].

MPV AND SMOKING

Butkiewicz et al. designed a study to assess platelet parameters in smoking healthy subjects with reference to sex. In the group of women, 27% were smokers, in the group of men 49%. Irrespective of gender the smoking did not have any effect on

the following parameters: mean platelet volume, percentage of large platelets, concentration of thrombopoietin, absolute count of reticulated platelet and concentration of thromboglobulin.

Slavka et al.[35], in their study concluded that increased MPV may carry increased risk of mortality due to ischemic heart disease which was as much as that due to smoking or obesity[22].

MPV AND ISCHEMIC HEART DISEASE

Khandekar et al.[23] studied a total of 210 cases, 94 patients had unstable angina (UA) or acute myocardial infarction (AMI), 70 patients had stable coronary artery disease (stable CAD) or were admitted for a coronary angiography or coronary artery bypass graft procedure and 30 age and sex matched healthy controls with no history of heart disease and a normal electrocardiogram. Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Platelet Large Cell Ratio (P-LCR)—were significantly raised in patients with AMI and UA (mean MPV, 10.43 (SD, 1.03) fL; mean PDW, 13.19 (SD, 2.34) fL; mean P-LCR, 29.4% (SD, 7.38%) compared with those with stable CAD (mean MPV, 9.37 (SD, 0.99) fL; mean PDW, 11.35 (SD, 1.95) fL; mean P-LCR, 22.55% (SD, 6.65%) and the control group (mean MPV, 9.2 (SD, 0.91) fL; mean PDW, 10.75 (SD, 1.42) fL; mean P- LCR, 20.65% (SD, 6.14%).

Agrawal et al.[24] concluded that MPV was significantly higher in patients with AMI in comparison to the control subjects. However, there was no significant difference in MPV values of patients with ST elevation and non ST elevation MI. When atherosclerotic plaque ruptures or erodes; platelets are recruited to the exposed sub endothelial region and partially occluded vessel becomes completely occluded with the newly formed thrombus. Larger platelets have greater prothrombotic potential and are biologically more potent. Increased platelet volume has been shown to be more reactive with greater production of thromboxane A2, and serotonin. These are mechanisms by which platelets contribute to development of myocardial infarction via platelet mediated vasoconstriction and inflammation.

In fact Huczek et al.[25] observed that abciximab (GPIIb/III a antagonist) reduced mortality significantly only in patients of myocardial infarction who had high MPV.

Martin et al. also found that greater MPV correlated with subsequent mortality and nonfatal myocardial reinfarction[26].

Pereg et al. revealed that thrombolytic failure rate in STEMI was significantly higher in patients with high MPV[27.]

MPV AND STROKE

Bath et al. in a sub-study of The Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial followed 3134 individuals for an average of 3.9 years and assessed the association of MPV with the risk of stroke. MPV was positively associated with the risk of stroke, with an 11% increased relative risk (95% CI, 3% to 19%) of stroke per femtoliter greater MPV. There was no clear association of MPV with the risk of major coronary events (9% decreased relative risk; 95% CI, 23% to 7%). Perindopril did not alter MPV. This study concluded that MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or transient ischemic attack[28].

Shahab et al. concluded that Increased MPV has been observed as independent of other established determinants and have seen the association of ischemic stroke with increased MPV in diabetic patients. However, this doesn't apply to haemorrhagic strokes or strokes of unknown etiology[18].

MPV IN TYPE 2 DIABETES MELLITUS

Kodiatte et al. studied 166 male diabetics and 89 female diabetics in the study (255 in total). There were 145 non-diabetic males and 106 non-diabetic females in the study (251 in total). MPV was higher in diabetics compared to the non-diabetic subjects [8.29 ± 0.74 fl versus 7.47 ± 0.73 fl (P= 0.001), respectively. MPV showed a strong positive correlation with FBS, PPBS and HbA1C levels (P=0.001). No statistical correlation was seen between MPV and the duration of DM, BMI and the vascular complications in the diabetic group. In the diabetic group, the mean MPV in subjects with complications (8.35±0.73 fl) were higher than that of subjects without complications (8.2±0.74 fl) but independent student t-test did not show any statistical significance[29].

Hekimsoy et al. studied MPV in diabetics. MPV was measured in 145 consecutive Type 2 diabetic patients and 100 non-diabetic control subjects. MPV was significantly higher in diabetics compared to non-diabetic healthy controls [10.62+/-1.71 fl vs. 9.15+/-0.86 fl (P=.00)], respectively[7].

Yenigün et al.[30] evaluated MPV in patients with type II diabetes mellitus (DM) and its association with diabetic microvascular and macrovascular complications. A total of 48 patients with type II DM and 30 age and gender matched healthy subjects constituted the study population. 12 of the diabetics (25 %) had macrovascular complications, 26 patients (54.2 %) had HT, 15 patients (31.3 %) had retinopathy, 16 patients (33.3 %) had nephropathy and 39 patients (81.2 %) had neuropathy. Mean HbA1c was 8.73 ± 2. MPV was significantly higher in patients with type II DM than the healthy controls (9.25 ± 1.49 and 8.47 ± 0.49, respectively) (p & le; 0.01). The diabetic patients were divided into subgroups depending on the presence of microvascular complications. Patients with at least one of the microvascular complications had slightly higher MPV compared to the ones without any of the complications (9.38 ± 1.47 fl and 7.85 ± 0.88 fl, respectively) (p= 0.048). In type II diabetic patients there was no association between MPV and age, duration of diabetes, lipid profile, HbA1C, and FBS[30,31].

MECHANISM

Platelets from patients with diabetes express more surface P-selectin and glycoprotein (GP) IIb /IIIa receptors leading to the initial step in platelet aggregation, that is adhesion of platelets or platelet shape change. This platelet shape change is reflected in change of mean platelet volume and are more sensitive to agonist stimulation than platelets from patients without diabetes[32]. Platelets in DM have dysregulated signaling pathways that lead to an increased activation and aggregation in response to a given stimulus (platelet hyper-reactivity)[33,34]. DM has been considered as a "prothrombotic state" with increased platelet reactivity[35]. Platelet hyperactivity has been reported in diabetics and animals, both in vivo and in vitro[36,37].

Platelet hyper-reactivity and increased baseline activation in patients with diabetes is Multifactorial[38,39]. It is associated with biochemical factors such as hyperglycemia and hyperlipidaemia, insulin resistance, an inflammatory and oxidant state and also with increased expression of glycoprotein receptors and growth factors. Hyperglycemia can increase platelet reactivity by inducing non enzymatic glycation of proteins on the surface of the platelet, by the osmotic effect of glucose and activation of protein kinase C. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate platelet function which is directly regulated by insulin via a functional insulin receptor (IR) found on human platelets[33,34,39].

In vivo experiments have confirmed that insulin inhibits platelet interaction with collagen and attenuates the platelet aggregation effect of agonists in healthy non-obese individuals.

In inflammation, superoxide increases intraplatelet release of calcium after their activation and thus enhancing platelet reactivity. Superoxide limits the biologic activity of nitric oxide (NO) because the oxidative stress impairs endothelial function that reduces production of NO and prostacyclin. Decreasing the effect of NO brings about increased platelet reactivity[3334,39].

Platelet activation contributes to the pathology by triggering thrombus formation and causing microcapillary embolization with the release of constrictive, oxidative, and mitogenic substances such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) that accelerate progression of local vascular lesions like the neovascularization of lens in diabetic retinopathies[32].

Larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and β-thromboglobulin, and produce more thromboxane A2 than smaller platelets[39,40,41]. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. There might be small bleeds due to the rupture of atherothrombotic plaques leading to increased platelet recruitment, hyper reactivity, and bone marrow stimulation. Hyperglycemia leads to a compatible osmolyte hypothesis in which there is injurious shift of the intracellular electrolytes and water into the platelets due to accumulation of sorbitol, myoinosital and taurine. This shift may increase the volume of the platelets. High MPV is emerging as a new risk factor for the vascular complications of DM of which atherothrombosis plays a major role[13].

MPV AND DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the most common and specific microangiopathy of diabetes mellitus (DM)[42]. There are clearly defined risk factors for DR, such as hyperglycemia, hypertension, dyslipidaemia, and diabetes duration[43]. It has also shown that functional and structural changes in retinal arterioles are also a risk factor for DR[44].

Mardiya Sari et al. found that PDR group had the highest MPV value compared than NPDR and normal fundoscopy group and also explained in diabetics sustained hyperglycemia leads to a series of interrelated alterations that can cause endothelial dysfunction and vascular lesion in diabetic complications. Formation of advanced glycalation end products, activation of protein kinase C and disturbance in polyol pathways are mechanisms by which increased glucose induces vascular abnormalities[45].

It can be explained because DM is a prothrombotic that chronically activate platelets, activate the coagulation system and decrease the ability of fibrinolysis. These phenomena, together with impaired prostanoid metabolism, phosphoinositide turn over and enhanced calcium mobilization contribute to enhanced risk of small vessel occlusions[45].

MPV value above the upper limit normal suggests that platelets in the circulation were younger, bigger and more reactive to aggregate because it will secrete more serotonin, â-thromboglobulin and produce more thromboxane A2 than normal platelets. This will produce a procoagulant effect and lead to vascular complications[45].

Orhan et al. concluded that Occlusions and micro aneurysms result in hypoxia in diabetic retinopathy which is a strong stimulus for new vessel formation. Vascular endothelial growth factor, which is released in response to hypoxia, strongly induces neovascularization. Platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, insulin like growth factor-1, growth hormone and basic fibroblast growth factor induce collagen synthesis and cause proliferative retinopathy via neovascularization. However, significantly increased levels of MPV in proliferative retinopathy suggest that growth factors released from activated platelets indirectly contribute to the disease progression[40].

Several studies have demonstrated that, platelets accumulate in retinal vasculature and induce the release of local growth factors by causing inflammation. In another study, an increased level of platelet derived growth factor in vitreous fluid of patients with proliferative DRP has been shown[46].

MPV AND DIABETIC NEPHROPATHY

Microalbuminuria is one of the earliest markers of diabetic nephropathy. Microalbuminuria (MA), a reversible phase of diabetic nephropathy, is also a disease risk, independent of risk factors both traditional (e.g., hypertension) and non- traditional (e.g., C-reactive protein).

Bayram et al. found that MPV levels were significantly higher in patients with T2DM having microalbuminuria than in the controls[47].

Zdrojewski et al., demonstrated non-diabetic patients with glomerular disease, spontaneous thrombocyte aggregation and MPV values were found to be increased[48].

Yarlioglues et al. demonstrated with primary hypertensives, urine albumin/creatinine ratio was found to be correlated with MPV[49].

Turgutalp et al. demonstrated positive correlation with serum creatinine and negative correlation with glomerular filtration rate with MPV in their diabetic nephropathic patients[50].

In Bavbek et al. study with type 2 diabetics, Creatinine Clearance in patients with high MPV values was lower than in patients with normal and low MPV values, and there was no difference between patients with normal and low MPV values[51].

MPV AND DIABETIC NEUROPATHY

Papans et al., concluded that mean platelet volume was significantly (p=0.03) higher in patients of group A (cases) (15.2+/- 1.6fl) than in those of group B (control) (11.3 +/-fl) and no association was observed in neuropathic patients between MPV and severity of neuropathy. Indeed, diabetes mellitus is thought to cause major disruption of severe metabolic and vascular mechanisms which contribute to development of neuropathy. For this reason despite some evidence of small role for platelet activation in pathophysiology of neuropathy there is much more to be determined[52].

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Review

Magnesium - An Essential Element, Vital for Human Health

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ABSTRACT

Magnesium is one of the four essential metals for human health vital for numerous physiological functions. Biologically, magnesium is considered a "chronic regulator" and a "forgotten electrolyte," essential for numerous cellular processes. It is central to the activity of around 500 enzymes known as kinases, which regulate complex cellular functions. It is vital for electrolyte homeostasis and plays a critical role in controlling neuromuscular function, regulating heart rhythm, modulating vascular tone, and influencing hormone secretion. Magnesium is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Deficiency in magnesium can lead to a range of health issues, including decreased bone density and an increased risk of various disorders.

KEYWORDS: Essential metal, Kinases, “Forgotten electrolyte”, Electrolyte homeostasis, "chanzymes"

INTRODUCTION

Magnesium is an essential element vital for numerous physiological functions that support overall health. Despite its importance, it often goes unrecognized as a major mineral. Magnesium is one of the four essential metals for human health, alongside calcium, potassium, and sodium, with a relatively high recommended daily allowance (RDA). Its absorption and retention decrease with age, making deficiency more common in the elderly. The magnesium content in drinking water also varies significantly, affecting dietary availability.

Magnesium plays a critical role in controlling neuromuscular function, regulating heart rhythm, modulating vascular tone, and influencing hormone secretion and NMDA release in the central nervous system. It acts as a second messenger in intracellular signaling and regulates cardiac clock genes that control circadian rhythms within biological systems. Magnesium functions in body fluids as hydrated ions, which significantly influence its electrochemical, biochemical, and physiological roles. Its unique ionic hydration form enhances its recognition and transport at the molecular level.

Biologically, magnesium is considered a "chronic regulator" and a "forgotten electrolyte," essential for numerous cellular processes. It is central to the activity of around 500 enzymes known as kinases, which regulate complex cellular functions, including signal transduction, energy production, and cellular communication. Magnesium-dependent kinases are involved in phosphorylation, crucial for activating proteins and other molecules. Magnesium is vital for electrolyte homeostasis, influencing the activity of various ATPase pumps and preventing conditions like hypokalemia and hypocalcemia.

Magnesium is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Deficiency in magnesium can lead to a range of health issues, including decreased bone density and an increased risk of various disorders. Causes of magnesium deficiency include poor dietary intake, excessive renal loss (often due to alcohol consumption), malabsorption, and certain medications. Clinicians often rely on laboratory tests for diagnosis, but lifestyle factors such as diet, exercise, and alcohol consumption can also indicate potential deficiencies. Identifying these factors is crucial for diagnosing and treating magnesium deficiency, which is linked to a wide range of pathologies[1].

Bioavailability and Absorption

Dietary magnesium has decreased due to changes in eating habits and food processing. High-magnesium foods include almonds, bananas, black beans, broccoli, brown rice, cashews, flaxseed, green vegetables, nuts, oatmeal, seeds, soybeans, sweet corn, tofu, and whole grains. Common sources include green vegetables, cereals, fish, nuts, and water, with hard water typically containing more magnesium than soft water. However, magnesium levels in water can vary greatly. Magnesium is abundantly found in foods, especially green vegetables due to its presence in chlorophyll. Daily intake varies from 6 to 20 mmol, with an average of about 12 mmol. Hard water can contain up to 5 mmol/L of soluble magnesium, which might be more bioavailable than magnesium in certain foods.

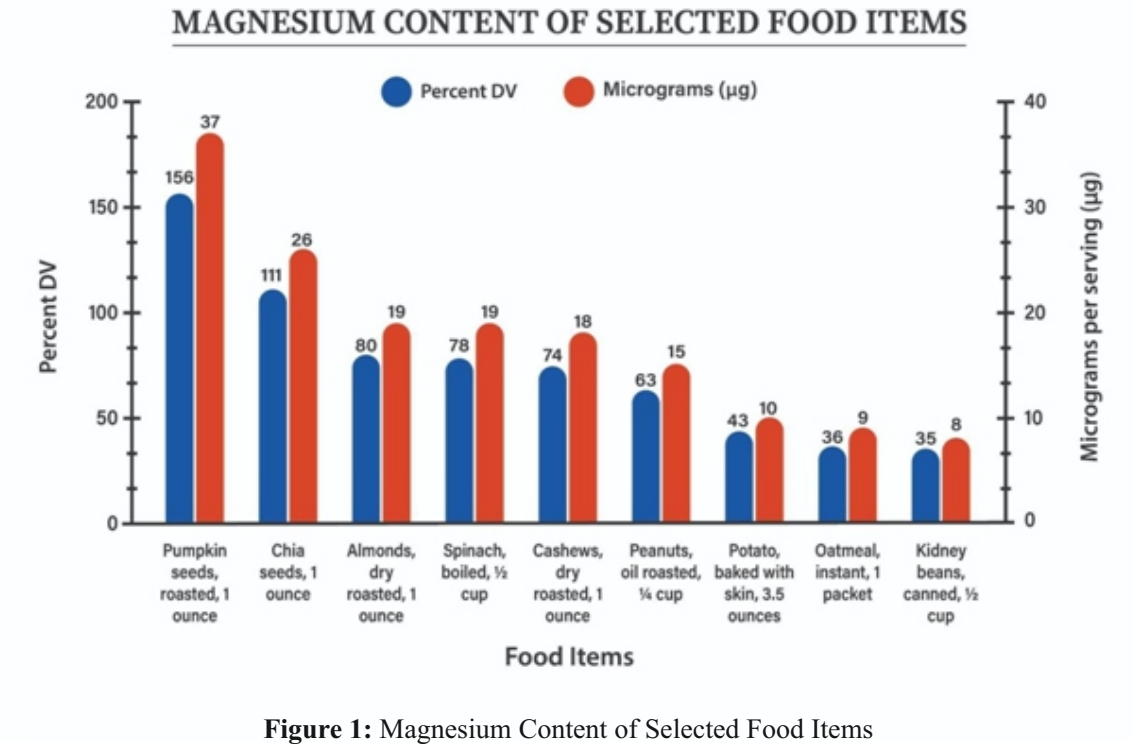

Figure 1: Magnesium Content of Selected Food Items

This figure shows the magnesium content in various food items, measured in both percent daily value (% DV) and micrograms (µg) per serving. The Daily Value (DV) for magnesium is 420 mg for adults and children age 4 years and older. Data for this figure was sourced from the National Institute of Health's Office of Dietary Supplements. [Magnesium Fact Sheet for Health Professionals]

Magnesium deficiency, affecting many cellular functions, is linked to systemic diseases. For instance, a study of over 286,000 individuals showed an inverse relationship between magnesium intake and type II diabetes incidence, suggesting increased consumption of magnesium-rich foods may reduce diabetes risk.

Magnesium is vital for electrolyte homeostasis, influencing the activity of various ATPase pumps, and preventing conditions like hypokalemia and hypocalcemia. It is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Magnesium deficiency can lead to a range of health issues, affecting bone density and increasing the risk of disorders.

Magnesium (Mg) absorption in the body primarily occurs in the small intestine, specifically in the ileum and the jejunum. This occurs through tight junctions between enterocytes (intestinal cells) and is driven by the concentration gradient. When dietary Mg is high, passive transport becomes more significant. This involves specific Mg transport channels and occurs mainly when dietary Mg is low. The primary channels responsible for Mg uptake are Transient Receptor Potential Melastatin (TRPM)6 and TRPM7. TRPM6 is primarily expressed in the distal small intestine and colon, while TRPM7 is more widely distributed and supports magnesium absorption. Once absorbed, Mg enters the bloodstream and is distributed to various tissues. Approximately 60% is stored in bones and 20% is located in muscles.

Magnesium homeostasis, crucial for many bodily functions, has only recently been understood in detail. Two ion channels, TRPM6 and TRPM7, have been identified as key players in magnesium transport and homeostasis. These channels, part of the Transient Receptor Potential Melastatin (TRPM) sub-family, facilitate magnesium absorption from the gut and reabsorption by the kidneys.

TRPM6 is primarily expressed in the colon and renal distal tubules, responding to low intracellular magnesium levels by increasing magnesium absorption and reabsorption. TRPM7 is more widespread, found in various organs like the lungs. These channels, termed "chanzymes" due to their dual channel and kinase functions, represent a molecular mechanism that regulates magnesium balance at the cellular level. In the gut, Mg2+ absorption primarily occurs in the distal ileum and colon via the Mg2+ channels TRPM6 and TRPM7.

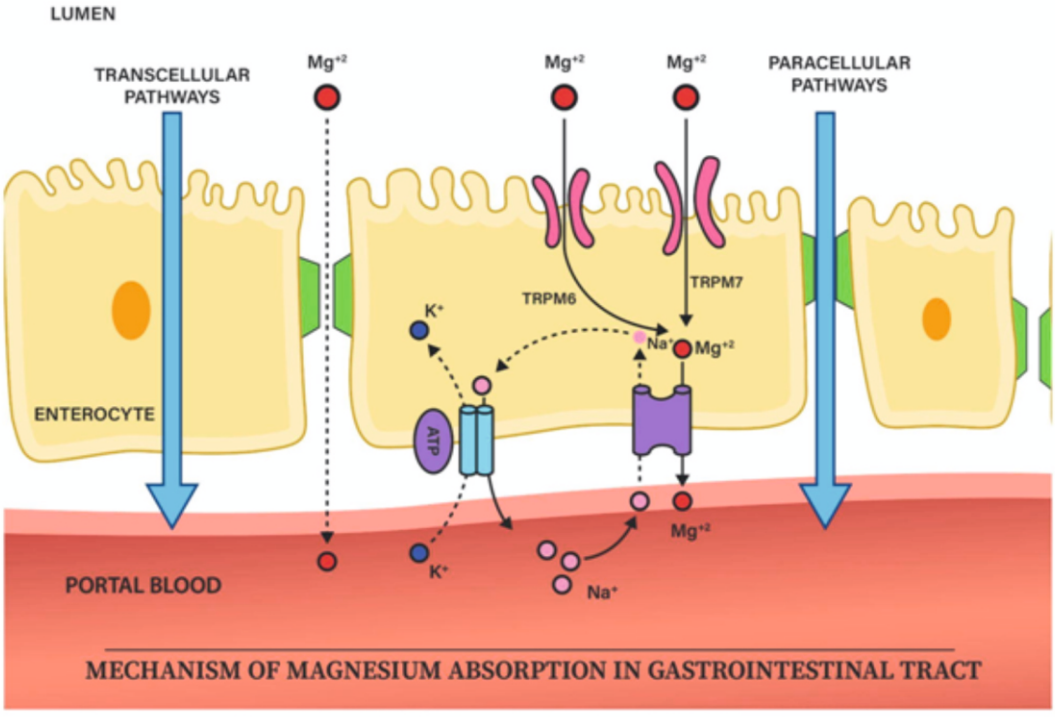

Figure 2: Mechanism of Magnesium absorption in gastrointestinal tract

TRPM6 and TRPM7 are members of the Transient Receptor Potential (TRP) channel family, specifically the TRPM (Melastatin) subgroup, and play critical roles in magnesium transport within enterocytes (intestinal cells).

The recommended daily intake of magnesium for adults is 300-400 mg/day, with absorption rates influenced by intake levels and overall body magnesium status. Dietary intake of magnesium is essential, with 30-70% absorbed by a healthy gut. Absorption occurs both actively and passively, with active uptake facilitated by TRPM6 and TRPM7 channels in the large intestine, and passive absorption in the small intestine [Figure 2]. Magnesium homeostasis is maintained through renal reabsorption and urinary excretion, with renal conservation occurring during deficiency and increased excretion during surplus. Despite renal adjustments, magnesium can be drawn from skeletal storage to maintain serum levels, which may lead to bone issues like osteopenia and osteoporosis. Magnesium is absorbed in the intestines via passive paracellular and active transcellular pathways. TRPM6 expression is influenced by factors such as acid-base status, 17-estradiol, β-adrenergic activity, FK506, and cyclosporine.

SGLT2 inhibitors, used to treat type II diabetes by increasing urinary glucose excretion, have been associated with higher serum magnesium levels. This suggests potential benefits of SGLT2 inhibitors may include altered magnesium homeostasis. Magnesium supplements, such as magnesium citrate, glycinate, threonate, and malate, are available, with organic forms being more bioavailable than inorganic ones. However, some studies report no significant differences in bioavailability among different formulations. Oral magnesium supplements can cause diarrhea, while transdermal applications, such as magnesium oil, may minimize this side effect and have shown benefits in conditions like diaper rash. Epsom salt baths are also used to alleviate various conditions, though excessive ingestion can lead to complications. Hypermagnesemia, although rare, can result from high doses of magnesium, leading to serious health issues like hypotension, bradycardia, and coma.

Individuals with serum magnesium around 1.82 mg/dL are likely deficient, while levels above 2.07 mg/dL are considered adequate. Red blood cell (RBC) magnesium levels are a better indicator of body magnesium status, with normal RBC levels ranging from 4.2 to 6.8 mg/dL[2].

Dietary Influences

- Food Processing: Common food processing methods, such as refining white flour or rice, can reduce Mg content by 300–400%.
- Phytic Acid: Found in nuts, seeds, and grains, it can chelate and diminish the absorption of essential minerals like Ca, Fe, Mg, and Zn.
- Glyphosate: The widely used pesticide can chelate minerals, potentially affecting their availability.
- Traditional Foods: Consuming traditional foods and using methods like sourdough fermentation can improve Mg bioavailability[3].

The Institute of Medicine (IOM) sets the upper tolerable limit for Mg supplementation at 350 mg/day to avoid gastrointestinal side effects. Individuals with renal impairment are at higher risk for Mg toxicity and should be closely monitored. Gastrointestinal symptoms often indicate excessive Mg levels, but the severity can vary based on the type of Mg salt ingested. Awareness of potential toxicity is crucial, especially for those with compromised kidney function. The lack of practical training in clinical nutritional biochemistry within medical education is a major issue contributing to widespread Mg insufficiency. Mg supplementation is beneficial for conditions such as preeclampsia/eclampsia, cardiac arrhythmias, migraine headaches, metabolic syndrome, diabetes and its complications, premenstrual syndrome, hyperlipidemia, and asthma. No specific hormone regulates Mg, but several hormones (e.g., insulin, PTH, calcitonin, catecholamines) influence Mg homeostasis.

Maintaining Mg sufficiency can significantly impact many common clinical conditions. The lack of practical training in clinical nutritional biochemistry within medical education is a major issue contributing to widespread Mg insufficiency. Higher requirements in conditions like pregnancy, aging, exercise and certain diseases (e.g., type 2 diabetes). High intake of sodium, calcium, protein, alcohol, caffeine, and certain drugs (e.g., diuretics, proton-pump inhibitors) can alter Mg balance. Mg absorption primarily occurs in the small intestine. Daily Mg intake needed: 5–7 mg/kg. Kidney excretes about 120 mg of Mg daily, with reabsorption increasing during Mg depletion[4].

Food processing often reduces magnesium content in cereals and carbohydrate products. The broad reference range for 24-hour urinary magnesium excretion (2.0–7.5 mmol) mainly

reflects dietary variations.

Typically, of the 12 mmol of dietary magnesium, about 6 mmol is absorbed, primarily in the small intestine. Absorption occurs via two mechanisms: an active transport system that saturates at low concentrations and a passive diffusion system that consistently absorbs around 7% of ingested magnesium. Some magnesium can also be absorbed in the large intestine, as evidenced by hypermagnesaemia from magnesium-containing enemas. Approximately 2 mmol of magnesium is secreted into the intestine, resulting in a net absorption of about 4 mmol per day, which is balanced by urinary excretion[5].

Excretion

Magnesium homeostasis is primarily managed by filtration and reabsorption in the kidneys. When magnesium intake is high, urinary excretion increases, and when intake is low, the kidneys conserve magnesium. Typically, 1000 mmol of magnesium is filtered daily, with only 3 mmol excreted in urine. About 10-15% of filtered magnesium is passively reabsorbed in the proximal tubule, while 65% is reabsorbed in the thick ascending loop of Henle via a paracellular mechanism involving paracellin-1, which is dependent on NaCl absorption. Factors disrupting NaCl "chanzymes" reabsorption, like diuretics and fluid expansion, enhance magnesium excretion. Additionally, 10-15% of filtered magnesium is actively reabsorbed in the distal tubule, regulated by divalent cation-sensing receptors, which adjust reabsorption based on plasma magnesium levels [Figure 3]. Hormones such as parathyroid hormone, glucagon, calcitonin, and insulin can increase magnesium reabsorption. Factors like hypercalciuria, hypophosphatemia, and metabolic acidosis also affect magnesium reabsorption, with metabolic acidosis linked to increased urinary magnesium loss, potentially reducing magnesium status in individuals on Western diets.

The blood Mg2+ concentration is regulated through a coordinated process involving intestinal Mg2+ absorption, storage in bones and soft tissues, and renal excretion. Similar to Ca2+, bone is traditionally viewed as the main storage site for Mg2+, containing 50% of the body's Mg2+ content. However, the role of soft tissues, such as muscles and the liver, in Mg2+ storage has gained recognition in recent years.

The proximal tubule (PT) is primarily responsible for the bulk reabsorption of Na+, K+, and Ca2+, but it only reabsorbs 20-30% of the filtered Mg2+ load. When the tubular fluid-to-ultrafiltrate concentration ratio exceeds 1.9 in the late PT, Mg2+ is reabsorbed through a passive paracellular mechanism which reabsorbs 15-25% of filtered Mg2+ mainly through paracellular transport. In the nephron, about 70% of plasma Mg2+ is filtered through the glomerulus. The majority of Mg2+ reabsorption occurs paracellularly, where ions pass between cells, while a smaller fraction is reabsorbed transcellularly, where ions move through the cells [Figure 3]. Magnesium ions (Mg^{2+}) are reabsorbed through solvent drag, where they move along with water via paracellular pathways. Mg^{2} can also passively diffuse from the tubule lumen into the interstitial space.

Proximal Tubule (PT) Magnesium Reabsorption

In the Proximal Convoluted Tubule (PCT), various transporters and channels are crucial for ion and water reabsorption. The NHE3 (Na^{+}/H^{+} Exchanger) facilitates sodium reabsorption by exchanging sodium for hydrogen, while the Na^{+}-K^{+} ATPase pump maintains the electrochemical gradient by pumping sodium out of the cell and potassium into the cell. Aquaporin-1 (AQP1) channels enable water reabsorption, and Kir4.2/Kir5.1 channels manage potassium recycling. Claudin 1/2 proteins are implicated in the paracellular transport of magnesium, though their precise role is unclear. The proximal tubule primarily reabsorbs sodium, potassium, and calcium, but handles only 20-30% of the filtered magnesium load. Initial studies indicated minimal magnesium transport in the early proximal tubule, with passive reabsorption occurring in the late proximal tubule when the tubular fluid-to-ultrafiltrate concentration ratio exceeds 1.9. Clinical studies emphasize the significance of proximal tubule glucose transport in magnesium reabsorption.

Magnesium (Mg^{2+}) Reabsorption and Regulatory Mechanisms in the Thick Ascending Limb (TAL)

The Thick Ascending Limb (TAL) of the Loop of Henle is the primary site for magnesium (Mg^{2+}) reabsorption, handling 50-70% of the filtered Mg^{2+} load via paracellular pathways. This process is facilitated by the cation-selective claudins, CLDN16 and CLDN19. Mutations in these genes cause familial hypomagnesemia, hypermagnesiuria, and nephrocalcinosis (FHHNC). The lumen-positive transepithelial membrane potential, generated by NKCC2 activity and potassium backleak through the ROMK channel, drives paracellular Mg^{2+} reabsorption. Inhibition of NKCC2 by furosemide reduces Mg^{2+} reabsorption in the TAL.

Research using isolated perfused TAL tubules has shown that deleting CLDN16 reduces the Mg^{2+} and Ca^{2+} permeability-to-Na^{+} permeability ratios, underscoring its role in Mg^{2+} reabsorption. TAL tight junctions exhibit a mosaic pattern where CLDN10b and CLDN16/19 are expressed separately, with CLDN10b forming monovalent cation pores and CLDN16/19 forming Ca^{2+}/Mg^{2+}-selective pores.

Common variants in CLDN14 are linked to differential Mg^{2+} and Ca^{2+} excretion. Although CLDN14 expression is low in the kidney, it is induced by high Ca^{2+} levels through the Ca^{2+}-sensing receptor (CaSR). Over expression of CLDN14 in the TAL decreases plasma Mg^{2+} and increases Mg^{2+} excretion, suggesting a regulatory role for CLDN14.

The NKCC2 (Na^{+}-K^{+}-$2Cl^{-}$ Co-transporter) and ROMK channels are essential for TAL function. NKCC2 transports Na^{+}, K^{+}, and Cl^{-} from the lumen into cells, while ROMK recycles K^{+} back into the lumen. The Na^{+}-K^{+} ATPase pump maintains Na^{+} and K^{+} gradients, and ClC-Kb and Barttin channels facilitate chloride reabsorption. Although the CaSR regulates divalent cation reabsorption, its specific impact on Mg^{2+} reabsorption in the TAL is not clear. Gain-of-function mutations in CaSR can inhibit NKCC2 activity, leading to hypomagnesemia and hypocalcemia.

Parathyroid hormone (PTH) significantly enhances Mg^{2+} reabsorption in the TAL, with low serum Mg^{2+} levels common in hypoparathyroidism. Mutations in the RRAGD gene, which affect the mTOR complex 1 (mTORC1) pathway, are linked to autosomal dominant hypomagnesemia. Hyperactivation of mTORC1 influences Mg^{2+} and Ca^{2+} reabsorption in the TAL, and mTORC1 inhibition is associated with hypomagnesemia and reduced NKCC2 expression, indicating a complex regulatory role for

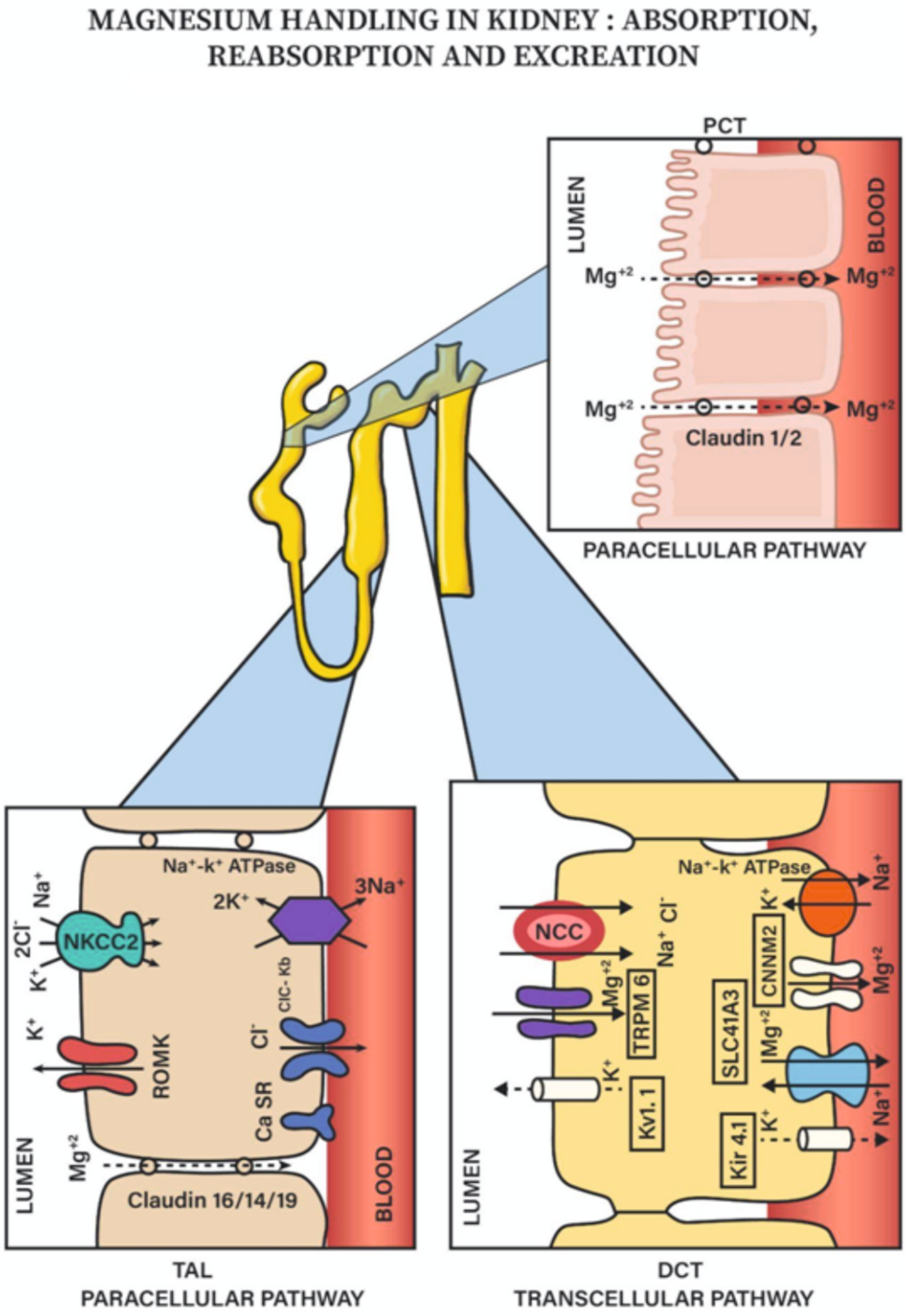

Figure 3: Mechanisms of Magnesium Handling in the Kidney

The diagram shows magnesium (Mg^{2+}) transport in the nephron. In the Proximal Convoluted Tubule (PCT), Mg^{2+} is reabsorbed via the paracellular pathway with Claudin 1/2. The Thick Ascending Limb (TAL) involves Claudin 16/14/19, NKCC2 (Na^+-K^+-$2Cl^-$ co-transporter), ROMK (renal outer medullary potassium channel), and ClC-Kb (chloride channel). The Distal Convoluted Tubule (DCT) features TRPM6 (transient receptor potential melastatin 6), NCC (sodium-chloride co-transporter), Kv1.1 (voltage-gated potassium channel subfamily A member 1.1), SLC41A3 (sodium-magnesium exchanger), CNNM2 (sodium-magnesium exchanger 1), and Kir4.1 (inwardly rectifying potassium channel subfamily J member 10).

Mg^{2+} Reabsorption and Regulatory Mechanisms in the Distal Convoluted Tubule (DCT)

In the Distal Convoluted Tubule (DCT), the NCC (Na^+-Cl^- Co-transporter) and other channels manage the reabsorption of sodium (Na^+), chloride (Cl^-), and magnesium (Mg^{2+}). The TRPM6 channel is crucial for transcellular Mg^{2+} reabsorption, with its activity enhanced by Epidermal Growth Factor (EGF). Mutations in TRPM6 cause familial hypomagnesemia with secondary hypocalcemia, leading to muscle cramps and seizures. TRPM7, often forming heterotetramers with TRPM6, also plays a role in Mg^{2+} reabsorption, with pathogenic variants linked to hypomagnesemia.

Kv1.1, encoded by the KCNA1 gene, supports TRPM6-mediated Mg^{2+} reabsorption by maintaining the electrochemical gradient. TRPM6/7 activity is influenced by intracellular Mg^{2+}, Mg-ATP, fluid shear stress, and hormonal regulators like EGF, insulin, estrogens, and β-adrenergic signaling. EGF increases TRPM6 membrane expression and is essential for Mg^{2+} homeostasis.

Basolateral Mg^{2+} transport involves proteins like CNNM2 and the solute carrier 41 protein family (SLC41A1−SLC41A3). CNNM2 is a candidate for Mg^{2+} extrusion, though its exact function is debated. SLC41A3 is enriched in the DCT, and knockout mice show hypomagnesemia. Na^+/K^+ exchange proteins, such as Na^+-K^+-ATPase subunits and Kir4.1/Kir5.1 K^+ channels, are vital for Mg^{2+} reabsorption, with mutations causing syndromes like EAST/SeSAME and Gitelman, leading to hypomagnesemia.

Mitochondrial function also plays a role in Mg^{2+} reabsorption, with mutations in mitochondrial tRNAs and tRNA synthases linked to hypomagnesemia. The DCT adapts to Na^+ or Mg^{2+} wasting by increasing its reabsorptive capacity in response to stimuli like diuretics or dietary restrictions. Further research is needed to fully elucidate the molecular processes involved in Mg^{2+} transport in the DCT[6].

Crucial Role of Magnesium in Neuronal Development and Neurological Disorders

Magnesium (Mg^{2+}) is crucial for various diseases, including cancers, diabetes, and neurodegenerative disorders like Parkinson's, Alzheimer's, and demyelination diseases. Its regulation is complex, leading to ongoing debates in research. However, Mg^{2+} plays essential roles in neuronal development, normal functioning, and disease states. Mg^{2+} supplementation often has neurotrophic effects, indicating that maintaining Mg^{2+} balance could be a potential therapeutic target for neuronal diseases.

In the central nervous system (CNS), the extracellular fluid (ECF) is separated from the blood by the blood-brain barrier (BBB). The BBB, made up of brain capillary endothelial cells, regulates the passage of nutrients and electrolytes to maintain ECF homeostasis. Due to the close proximity of neuronal and glial cells (20 to 50 nm apart) and the small volume of extracellular space in the brain, ECF component concentrations fluctuate significantly. Therefore, the BBB actively transports various molecules to maintain ECF stability. ECF Mg^{2+} concentrations are higher than those in plasma or cerebrospinal fluid (CSF), indicating active Mg^{2+} transport across the BBB [Figure 4]. In vitro models of the BBB with human brain endothelial cells have shown the presence of active Mg^{2+} transporters, such as transient receptor potential melastatin 7 (TRPM7) and MagT1. However, the mechanisms of Mg^{2+} transport in the BBB are not well understood. Research has mainly focused on Mg^{2+} absorption and excretion in the small intestine and kidneys, so further studies are needed to explore these processes in the CNS. Additionally, gap-junction-mediated cytosolic Mg^{2+} ([Mg^2] cyto) regulates the circadian rhythm of BBB permeability in Drosophila, suggesting that intracellular Mg^{2+} levels in the BBB affect the neuronal environment in the brain.

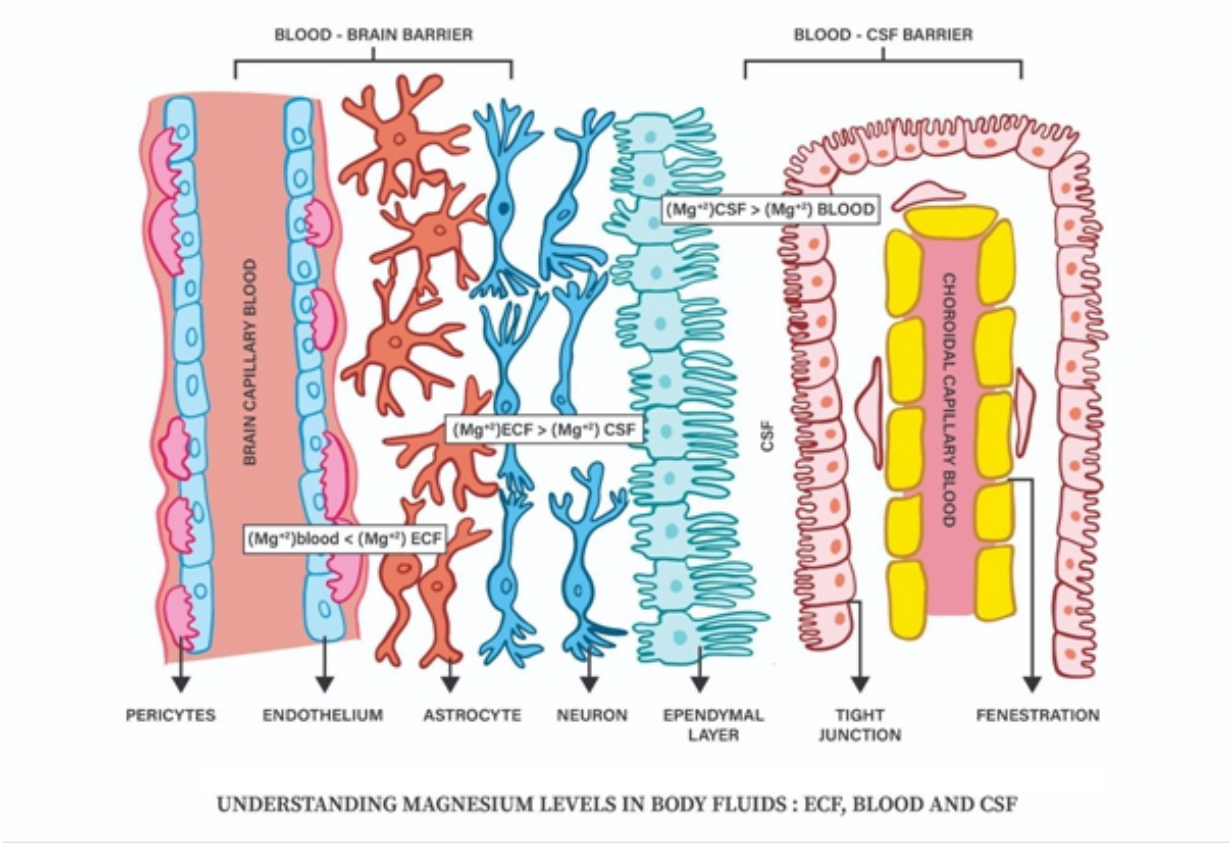

Figure 4: Understanding Magnesium Levels in Body Fluids
The diagram illustrates magnesium (Mg^{2+}) distribution across the blood-brain barrier, blood-cerebrospinal fluid (CSF) barrier, and within extracellular fluid (ECF), highlighting the higher Mg^{2+} concentration in ECF compared to blood, and in CSF compared to blood.

Cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, exists in a normal adult human body at about 100 to 150 mL It serves as a mechanical barrier and is produced by the filtration of blood and active transport of molecules such as nutrients, hormones, metal ions, and metabolites across the ependymal cells in the choroid plexus at a rate of 0.2 to 0.7 mL per minute. CSF Mg^{2+} concentrations are higher than those in blood, indicating active Mg^{2+} transport from the blood into CSF. Changes in CSF Mg^{2+} levels correlate with extracellular Mg^{2+} around neurons, affecting neural activities. Thus, CSF Mg^{2+} is closely related to various brain functions. Notably, CSF Mg^{2+} levels and cognitive functions have shown a positive correlation. Additionally, intracellular Mg^{2+} levels in erythrocytes significantly correlate with CSF Mg^{2+} in the hippocampus and with hippocampal synapse density and recognition and memory performance, suggesting that erythrocyte Mg^{2+} levels are a good indicator of recognition and memory. These findings highlight the importance of Mg^{2+} homeostasis in the human body for brain functions, particularly synaptic connectivity.

The magnesium concentration in cerebrospinal fluid (CSF) is 1.3 times higher than in the blood. This indicates a selective transport mechanism at the choroid plexus epithelium. Magnesium concentration in the extracellular fluid is higher than in the blood but lower than in the CSF[7].

Cellular Distribution and Physiological Roles of Magnesium

Magnesium (Mg2+) stands as the most abundant divalent cation within mammalian cells, with a total concentration typically ranging between 17 and 20 mM . Maintaining a relatively stable gap between the cytosolic magnesium concentration ([Mg2+] cyto) and extracellular free magnesium concentration ([Mg2+] ex) is vital, usually within less than twofold. Despite the

electrochemical equilibrium suggesting a resting concentration of 50 mM for Mg2+ in the cytosol, only a slight change in [Mg2+] cytosol is observed even under conditions of Mg2+ mobilization. Cells employ various mechanisms to maintain intracellular magnesium within a narrow range, balancing influx, efflux, and stored magnesium levels. Mg2+ transport requires considerable energy due to its unique properties, including tight binding to water molecules and a large hydrated radius compared to its ionic radius. Although several Mg2+-transporting proteins are identified, their association with neurophysiology remains largely unexplored.

Cellular Distribution

1. *Cytosol*
   Mg2+ in the cytosol forms complexes with a wide array of biomolecules, with adenosine 5′-triphosphate (ATP) serving as a major intracellular pool due to its abundance and high binding affinity . Fluctuations in [Mg2+]cyto, even minor ones, can significantly impact cellular processes due to changes in the distribution of Mg-complexed biomolecules.

2. *Nuclei*
   Nuclear magnesium concentration ([Mg2+]nuc) varies depending on physiological conditions, with Mg2+ playing a crucial role in neutralizing the negative charges of chromatin, nucleic acids, and free nucleotides. [Mg2+]nuc affects cell mitosis, chromatin folding, and gene expression regulation.

3. *Mitochondria*
   Mitochondria serve as a major cellular magnesium pool and are key regulators of intracellular magnesium homeostasis. Mg2+ in mitochondria influences various functions, including mitochondrial energy metabolism, the apoptotic process, mitochondrial calcium homeostasis, and mitochondrial DNA functions.

4. *Endo(sarco)plasmic Reticulum*
   The endoplasmic reticulum (ER) accumulates Mg2+ and contributes to intracellular magnesium homeostasis. Mg2+ inhibits inositol-1,4,5-trisphosphate receptors (IP3R) and ryanodine receptors (RyR), which play essential roles in Ca2+ signaling in neurons.

5. *Ribosomes*
   Ribosomes, essential for protein synthesis, chelate significant amounts of Mg2+ and are closely associated with cytosolic magnesium levels. Mg2+ regulates protein synthesis via its effects on ribosomal functions through the mechanistic target of rapamycin (mTOR) pathway.

Physiological Roles of Cellular Mg2+

Magnesium interacts with numerous biomolecules, serving as a modulator of enzymatic activities, a cell protector against stress, a regulator of ion channels, and a stabilizer of DNA/RNA structures. Dysregulation of Mg2+ homeostasis is implicated in various diseases, including neurodegenerative diseases, diabetes mellitus, and metabolic syndrome.
Intracellular Mg^{2+} plays crucial roles in various biochemical processes due to its ability to neutralize negatively charged biomolecules like RNA/DNA, reactive oxygen species (ROS), and ATP. It acts as a counterion for these molecules, ensuring their stability and functionality. Dysregulation of Mg^{2+} homeostasis is linked to several disease conditions, including neurodegenerative diseases, diabetes mellitus, and metabolic syndrome.

Biochemical Reactions in Cells
Mg^{2+} influences over 600 enzymatic reactions, particularly those involved in energy metabolism, protein synthesis, and signal transduction. Its presence is essential for ATP-related biochemical reactions, as it stabilizes ATP molecules. Fluctuations in intracellular Mg^{2+} levels affect the energetic of these reactions. Mg^{2+} also competes with other ions like Ca^{2+} and protons, impacting cellular biochemistry in organelle-specific manners.

Intracellular Signaling
Mg^{2+} enhances the activity of protein kinases and thus modulates intracellular signal transduction. While its role as a second messenger has been debated, Mg^{2+} mobilization in response to biological stimuli suggests its involvement in cellular responses. Mg^{2+} regulates cellular processes in a cell-type specific manner and may function as a signal amplifier, particularly in neural development and plasticity.

Reactive oxygen species (ROS) Toxicity
Mg^{2+} suppresses the production of reactive oxygen species (ROS) in various tissues, including the brain. Its physicochemical properties allow it to react with ROS intermediates, protecting cells from oxidative damage.

Channel Regulation

Mg^{2+} regulates ion channels, such as the N-methyl-D-aspartate (NMDA) receptor in neurons. Its presence blocks the NMDA receptor, affecting neuronal excitability and neurotransmission.

DNA Protection and Genome Stability

Mg^{2+} stabilizes DNA and chromatin structures, protecting them from damage caused by ROS. It also serves as a cofactor in DNA replication and repair processes, ensuring accurate transfer of genetic information and maintaining genome stability.

In a nutshell, cellular Mg^{2+} plays diverse and essential roles in maintaining cellular function and homeostasis, impacting processes ranging from energy metabolism to DNA stability. Its dysregulation can lead to various pathological conditions, emphasizing the importance of maintaining adequate Mg^{2+} levels for overall health.

Formation of Neural Networks and Synaptic Activities

Role of Mg^{2+} in Neural Development

Mg^{2+} is crucial for cellular and tissue-level growth and differentiation. In developing neurons, neurotransmitter-induced increase in cytoplasmic Mg^{2+} mobilized from mitochondria stimulates mTOR activities, facilitating neural network maturation. mTOR activation promotes dendritic arborization and protein synthesis, essential for neurogenesis.

Involvement of TRPM7 Channel in Neuronal Development

TRPM7 channel plays a significant role in intracellular Mg^{2+} homeostasis. Its contribution to embryonic development remains debated, but studies suggest its involvement in Mg^{2+} transport and neural development. TRPM7-mediated Mg^{2+} influx is crucial for growth cone pathfinding and neurite outgrowth by enhancing mTOR activation while preventing axonal overgrowth via ROS regulation.

Regulation of Electrical and Chemical Synapses by Mg^{2+}

Mg^{2+} controls the strength of electrical gap junctions, influencing long-term plasticity.

Action potential-triggered Mg^{2+} influx coordinates chemical and electrical synaptic activities, contributing to synaptic plasticity and neural network formation.

Neural Cell Fate Determination

Magnesium-L-threonate (MgT) increases neural stem cell (NSC) numbers and promotes differentiation into neurons in vivo, but not in vitro.

Mg2+ levels decline during brain development, correlating with the sequence of NSC differentiation into neurons and glia.

TRPM7 channels are involved in the proliferation and migration of astrocytes via ERK and JNK signaling pathways, impacting neuronal cell proliferation and differentiation.

In short, Mg^{2+} plays diverse roles in neural development, including regulating mTOR activity, guiding neurite outgrowth, controlling synaptic strength, and influencing NSC fate determination. TRPM7 channels are central to Mg^{2+} homeostasis and contribute significantly to various aspects of neural development and function.

Role of Magnesium in Parkinson`s Disease

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by symptoms like tremors and rigidity. These symptoms primarily arise from the loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. Recent research has highlighted the significant role of magnesium ions (Mg^{2+}) in PD pathology.

Low levels of Mg^{2+} in the cerebrospinal fluid (CSF) of PD patients, along with evidence linking magnesium deficiency to a higher risk of developing PD, underscore the importance of this mineral in the disease. Additionally, mutations in Mg^{2+}-transporting proteins such as TRPM7 and SLC41A1 have been found in some familial PD cases, indicating a genetic link to magnesium dysregulation in PD.

Mg^{2+} has been shown to protect dopaminergic neurons from neurotoxicity caused by toxins like MPP+, suggesting it has a neuroprotective role. Furthermore, impaired Mg^{2+} influx has been associated with reduced cell viability in PD models, highlighting the critical role of Mg^{2+} homeostasis. Mg^{2+} also directly inhibits the aggregation of α-synuclein, a protein closely linked to PD pathology, suggesting its potential therapeutic importance in slowing PD progression.

These findings collectively emphasize the multifaceted role of Mg^{2} in PD, suggesting further research and potential therapeutic strategies targeting Mg^{2+} dysregulation could be beneficial in managing PD. Mutations in Mg^{2+}-transporting proteins, low Mg^{2+} levels, and impaired Mg^{2+} influx are correlated with neuronal toxicity and α-synuclein aggregation,

key aspects of PD pathology.

Role of Magnesium in Alzheimer's Disease

Alzheimer's disease (AD) is characterized by the accumulation of amyloid β (Aβ) plaques and hyperphosphorylated tau proteins, leading to neuronal degeneration and cognitive decline, especially in individuals over 65 years old. AD patients often exhibit lower levels of Mg^{2+} in cerebrospinal fluid and brain tissue, correlating with more severe symptoms. Mg^{2+} deficiency is linked to emotional memory dysfunction, while Mg+2 supplementation improves learning, memory, and cognitive function, even after brain injury. In AD pathology, Aβ accumulation is influenced by extracellular Mg^{2+} levels, with higher Mg^{2+} concentrations preventing Aβ-induced reduction of synaptic NMDA receptors. MgT treatment reduces Aβ aggregation and neuronal toxicity, preventing cognitive deficits and synaptic loss in transgenic mouse models of AD. Additionally, Mg^{2+} in the blood-brain barrier reduces Aβ influx and promotes its clearance. MgSO4 treatment attenuates impairments in long-term potentiation and dendritic abnormalities in AD model rats by inhibiting GSK-3β and activating the PI3K/Akt signaling pathway. Furthermore, MgT suppresses inflammation triggered by Aβ oligomers by reducing TNF-α expression and inhibiting factors promoting Aβ synthesis, thus protecting neuronal function in AD pathology. Overall, Mg^{2+} influx appears to play a crucial role in mitigating the inflammatory mechanisms and preserving neuronal function in Alzheimer's Disease[8].

Association between Serum Magnesium and Type 2 Diabetes

The prevalence of diabetes has been escalating as an epidemic in India and world over. Magnesium plays a significant role in glucose and insulin metabolism and therefore, maintaining an appropriate level of serum magnesium is crucial for diabetic individuals[9]. There is a recognized relationship between serum magnesium levels and type 2 diabetes. Recent studies have indicated that low serum level of magnesium may contribute to insulin resistance and increases the risk of diabetes[10,11]. A retrospective, observational, cross-sectional study was conducted on 1694 patients. A linear regression analysis indicated associations between serum magnesium levels and fasting plasma glucose and HbA1c. The study found that serum magnesium levels decrease with increasing HbA1c. The exact mechanisms are not completely understood, but elevated urinary magnesium loss may account for observed low serum magnesium levels in diabetic patients with poor glycemic control[12].

Magnesium Deficiency: An Overview

Magnesium is a vital mineral involved in numerous bodily functions. It is essential for over 300 enzymatic reactions, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. Magnesium is also required for energy production, oxidative phosphorylation, and glycolysis.

Hypomagnesemia and Magnesium Deficiency

While hypomagnesemia (low serum magnesium levels) and magnesium deficiency (total body magnesium depletion) are often used interchangeably, they are not the same. A person can have normal serum magnesium levels despite total body magnesium depletion, and significant hypomagnesemia can occur without a total body deficit. Hypomagnesemia often goes undetected, with studies showing that only 10% of hypomagnesemic patients had magnesium requested for testing.

Etiology and Pathogenesis of Hypomagnesemia

1. Redistribution
   Hypomagnesemia can result from the shift of magnesium from extracellular fluid into cells or bones. This is seen in refeeding syndrome (in starved patients), treatment of metabolic acidosis and`Hungry bone syndrome` (post-parathyroidectomy or in patients with osteoblastic metastases)

2. Gastrointestinal Causes
   Pure magnesium deficiency from reduced dietary intake is rare in healthy individuals. It can occur in patients on magnesium-free intravenous fluids or total parenteral nutrition, particularly those with initially low serum magnesium. An inherited disorder of isolated magnesium malabsorption can cause hypomagnesemia with hypocalcemia, tetany, and seizures, usually presenting in infants with convulsions and other symptoms due to a mutation in the TRPM6 gene.

3. Renal Causes
   Proximal tubular reabsorption of magnesium is proportional to sodium reabsorption, and reductions in sodium reabsorption can lead to magnesium deficiency. Chronic renal failure can lead to obligatory renal

magnesium loss. In diuretic phase of acute renal failure, post-obstructive diuresis, and renal transplantation can also result in hypomagnesemia. Inherited disorders of renal tubular reabsorption of magnesium do exist but lack a consensus on classification.

4. Drugs

Several drugs, including antibiotics and chemotherapeutic agents, cause magnesium wasting.

Loop diuretics inhibit magnesium transport in the TAL, causing magnesium depletion, especially with long-term use. Thiazide diuretics, which act on the DCT, may not cause immediate magnesium wasting, but long-term use can lead to substantial depletion.

Cisplatin, a chemotherapy agent, frequently causes magnesium wasting, leading to hypomagnesaemia, hypocalciuria, and hypokalemia. The incidence of hypomagnesaemia increases with cumulative doses, with chronic hypomagnesaemia developing around three weeks after initial chemotherapy and usually persisting.

In a nut shell, hypomagnesaemia can arise from redistribution of magnesium within the body, reduced dietary intake, impaired intestinal absorption, increased gastrointestinal or renal loss, and the use of certain drugs. It often goes undetected but can have significant health impacts, particularly in acutely ill patients or those undergoing specific treatments.

Despite the normal serum range being 1.5 to 3.0 mEq/L, serum magnesium is a poor indicator of total body magnesium, as only a small fraction is present in serum. Magnesium distribution in the body is approximately 53% in bone, 27% in muscle, 19% in soft tissues, and just 3% in serum. Magnesium deficiency is relatively common, particularly among critically ill patients, with incidence rates reported as high as 65%. This deficiency significantly impacts mortality rates, as seen in the doubling of mortality in affected individuals.

Clinical Manifestations of Magnesium Deficiency

Biochemical Effects

1. Hypokalemia caused by renal potassium wasting and decreased intracellular potassium levels
2. Hypocalcemia results from impaired secretion of parathyroid hormone, resistance to its effects in the kidneys and bones, and resistance to vitamin D

Neuromuscular Symptoms

1. Tetany that causes spontaneous carpal-pedal spasms
2. Seizures
3. Movement Disorders: Vertigo, ataxia, nystagmus, as well as athetoid and choreiform movements
4. Muscle Issues: Muscular weakness, tremors, fasciculations, and muscle wasting
5. Psychiatric Manifestations: It include Mood and Cognitive Disorders, Depression and Psychosis

Cardiovascular Problems

1. Dysrhythmias: These includes ventricular tachycardia (*torsade de pointes*), atrial fibrillation, and supraventricular tachycardia
2. Hypertension and Vasospasm
3. ECG Changes: Prolonged QT and PR intervals, widened QRS complex, peaked T waves, and ST depression

Risk Groups for Magnesium Deficiency

1. Older Adults: Decreased dietary intake and absorption
2. People with Gastrointestinal Diseases: Conditions that impair absorption
3. Individuals with Type 2 Diabetes: Increased urinary loss
4. Alcoholics: Increased excretion and decreased absorption
5. People on Certain Medications: Diuretics, proton pump inhibitors, and some antibiotics
6. Athletes: Increased magnesium loss through sweat

Diagnosis of Magnesium Deficiency

- Clinical Assessment: Evaluation of symptoms and dietary intake
- Laboratory Tests: Serum magnesium levels, although these may not always accurately reflect total body magnesium stores

Treatment and Management

1. *Dietary Changes*: Increasing intake of magnesium-rich foods such as:
   - Green leafy vegetables (spinach, kale)
   - Nuts and seeds (almonds, sunflower seeds)
   - Whole grains (brown rice, quinoa)
   - Legumes (black beans, chickpeas)
   - Dairy products (milk, yoghurt)

- Fish (mackerel, salmon)
- Fruits (bananas, avocados)

2. *Supplementation*: Magnesium supplements may be recommended for those at risk of deficiency. Common forms include magnesium oxide, magnesium citrate, and magnesium chloride.

3. Addressing Underlying Conditions: Managing conditions that affect magnesium absorption or increase magnesium loss.

4. Lifestyle Modifications: Reducing alcohol intake, managing diabetes effectively, and being cautious with medications that affect magnesium levels.

Recommended Dietary Allowance (RDA)

The RDA for magnesium varies by age, sex, and life stage. For adult men, it is 400-420 mg per day, and for adult women, it is 310-320 mg per day. Higher amounts are recommended for pregnant (350-360 mg/day) and lactating women (310-320 mg/day).

Prevention

- Balanced Diet: Consuming a variety of magnesium-rich foods
- Awareness of Magnesium Inhibitors: Reducing intake of magnesium inhibitors like excessive alcohol and certain medications
- Supplementation When Necessary: Using magnesium supplements in populations at risk for deficiency

Magnesium deficiency can lead to a range of health issues, particularly affecting muscle and nerve function, cardiovascular health, and metabolic processes. Ensuring adequate magnesium intake through diet or supplements is crucial for maintaining overall health and well-being [13].

CONFLICTS OF INTEREST: None

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Review

Behavioural Addiction - A Short Review

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ABSTRACT

In the past few years especially with the inception of COVID-19 and subsequent lockdown periods, there has been increasing diagnostic concern around the compulsive or excessive use of various activities especially the digital ones and their potential to induce mental health problems besides the use of psychoactive substances. However, problematic or excessive uses of some of these activities are still goes unnoticed due to the overlapping conceptualisations. The current classificatory systems on psychiatric disorders diagnose certain conditions characterized by repetitive reward seeking behaviours that mimic with the most of the criteria for substance addiction and hence called behavioural addictions. The present review addresses these issues on conceptualisations of the phenomena within the research literature. The concepts or the phenomenon were extracted from various existing literature and subsequently content analysis method was utilized to analyse the concept. Furthermore, the current review also addresses a number of conceptualization shortcomings resulting from existing phenomenology, recent updates in classificatory systems and use of psychotherapeutic approaches on behavioural addictions.

KEYWORDS: Behavioural addiction, Conceptualization, Mental health, Digital use

The excessive uses of various activities which induce short term relief or reward have historically been conceptualized as either an impulsive trait or compulsive spectrum conditions. Currently these conditions are known as non-substance or 'Behavioural Addictions' (BAs). In response to recent revisions to the diagnostic criteria for addictive disorders within the DSM-5[1], there exists a pressing need for a comprehensive elucidation of behavioural addiction to chart a clear trajectory for future research and classification endeavours. Furthermore, a burgeoning body of scholarship has also substantially broadened the conceptual boundaries of behaviours and recreational pursuits

potentially characterized as behavioural addictions in the recent classificatory systems of mental disorders.

Conventionally, the term "addiction" has predominantly been conjoined with substance use disorders; however, a burgeoning interest has emerged in extending its purview to encompass BAs, characterized by compulsive engagement in gratifying activities yielding adverse consequences, sans psychoactive substance ingestion[2,3,4]. Several rationales have been advanced, advocating for the diagnostic legitimacy and clinical utility of behavioural addiction. From neurocognitive perspective, several distinct cognitive domains have been identified in patients with BAs suggesting a likely neurobiological overlap between BAs and substance addictions[5,6]. Neurocognitive deficits in response inhibition, performance monitoring and set shifting abilities are found to have trans-diagnostic markers of non substance addictive behaviours[5]. These neurocognitive findings suggest disrupted neural substrates and offer a new treatment paradigm to combat the symptoms of BAs[7]. More contemporarily, Robbins and Clark[8] have accentuated the shared psychobiological substrates underpinning both substance use disorders and BAs, intimating the potential efficacy of analogous intervention modalities.

The conditions of BAs have resulted in potential public health matters during the COVID-19 pandemic and have drawn considerable attention of government healthcare authorities. During the lockdown periods of Covid-19 pandemic, high prevalence rates of BAs and their potential health consequences were reported in most of the studies[9]. Especially the digital addiction has taken the precedence over all other daily activities[10]. Furthermore, several studies have revealed the association between BAs and other co-morbid psychiatric disorders[11,12]. The current scenario poses significant challenges in public health issues and hence necessitates the necessary adaptations in mental health service provision worldwide. However from global perspective, pathological gambling is most commonly encountered condition of behavioural addiction which had been included long back in the year 1980 in DSM-III. Since then the condition has seen several changes in its conceptualization with respect to its diagnostic classifications. Recently, the current version of DSM has introduced a dedicated chapter on 'Substance-Related and Addictive Disorders', spotlighting gambling disorder as the sole exemplar of an addictive disorder. Nevertheless, contention persists regarding the nosological status of other purported BAs.

Assessment Tools for BAs

Due to different conceptualisations and types of BAs, several psychological assessment tools in terms of structured clinical interviews and self rated inventories have been developed and used for assessing various types of BAs such as assessment of pathological gambling, computer/ internet addiction, workaholism, sexual addiction, compulsive buying and exercise[13]. However, there is lack of valid and reliable assessment tools available to assess certain types of BAs according to the diagnostic criteria of specific BA. When it comes to specific type of BA, the most commonly utilized tool is known as 'South Oaks Gambling Screen' (SOGS) which is known as a detailed screening tool for pathological gambling[14]. However, detailed evaluation of these behavioural addictions is commonly assessed through the use of self-report measure of 'FDAV' which is also known as 'Differentiated Assessment of Excessive Behaviours'[15]. There are a number of screening tools on BAs which cannot be described here in detail for the purpose of short review. Furthermore apart from the assessment, several characteristics have also been proposed to make the probable diagnosis of BAs[16].

Psychotherapeutic Approaches

With respect to the treatment of BAs, psychosocial interventions have also been found effective in reducing the symptoms besides pharmacological interventions[17]. Conventional therapeutic approaches to substance abuse, predicated upon the medical disease model, have historically marginalized psychological interventions, partly attributable to entrenched misconceptions surrounding psychotherapeutic modalities. Form psychoanalytic point of view, Wurmser's classical 'Psychoanalytic Conflict Model of Substance Abuse' provides valuable insights into addiction etiology, framing substance abuse as symptomatic of underlying fundamental psychodynamic conflicts, notably pertaining to an excessively punitive superego[18]. Substance consumption is construed as a coping mechanism deployed to mitigate overwhelming affective disturbances, furnishing a transient illusion of potency and efficacy. This conceptual framework underscores the imperative of addressing deeply ingrained intrapsychic conflicts in all kind of addiction treatment, supplementing conventional therapeutic modalities.

However in recent years, cognitive behaviour therapy (CBT), mindfulness based interventions (MBIs), and the trans-theoretical model have gained ascendancy[19,20,21]. With respect to the most utilized psychosocial management of BAs, cognitive-behavioural interventions have shown significant promising results in the treatment of BAs[22,23]. Cognitive-behavioural interventions, underpinned by robust empirical support, encompass a gamut of strategies ranging from social skills enhancement to relapse prevention, offering tangible benefits to affected individuals which have been largely adapted from psychotherapeutic manuals used in SUDs. However, Various CBT models and extensions have been developed to target BA symptoms. In a study, the therapeutic effectiveness of 'Multimodal school-based group CBT' was evaluated and findings suggest that group CBT holds promise as an effective intervention for addressing Internet addiction in adolescents[24]. In another study, a new CBT model for internet addiction known as 'cognitive behavioural therapy-Internet addiction (CBT-IA)' was developed for managing internet addiction, which incorporated harm reduction therapy along with CBT techniques[25]. Recently in India, a high prevalence of mobile

phone addiction has been observed in adolescents and young adults raising a significant concern of potential psychological harm in these population[26,27,28]. Several personality traits have also been identified in the population of BAs. Impulsivity, neuroticism and openness to experience traits were found to predispose an increased risk of Internet addiction[29,30]. These findings have implications for clinical practice and intervention strategies aimed at addressing Internet addiction among adolescents. Group CBT offers a structured and evidence-based approach to treating Internet addiction, providing adolescents with the tools and skills needed to manage their Internet use more effectively and maintain healthier behavioural patterns. Another important therapeutic approach known as the trans-theoretical model of behaviour change has also been applied independently as a psychological management in the field of BAs[31,32], two major aspects i.e. the stages of and the mechanisms of change[33]. The 'Transtheoretical Model of Change', elucidating the multifaceted journey toward addiction recovery, furnishes a cogent framework for understanding and guiding therapeutic interventions. Integration of psychoanalytic tenets into existing therapeutic modalities promises a more holistic and nuanced treatment approach, ameliorating the complex interplay of psychological factors endemic to substance abuse pathology.

Recently a surge in the use of MBIs has been observed for a variety of clinical conditions and considerable research evidence supports the efficacy of MBIs in BAs[34,35]. MBIs inculcate the stance of being non-judgemental in the present moment facilitating gentle awareness, observation and engagement with mental urges, impulses, cognitions and emotions attached with the addiction behaviours. A variety of mindfulness based approaches has been utilized and has shown considerable clinical efficacy in various types of BAs. Some empirical evidence is also available which corroborates the efficacy of psychoanalytic and interpersonal psychotherapeutic modalities in ameliorating addictive behaviours and pathological personality traits[36,37].

CONCLUSION

The term 'addiction' has long been studied with respect to a variety of SUDs. However in the past few years because of the existence of parallel diagnostic characteristics, an increasing research interest has been noticed in the area of BAs in terms of construct, assessment and psychotherapeutic management. The current review highlights the various assessment tools and effective interventions for BAs. Especially with respect to high prevalence rate of internet addiction in adolescents, various modifications of CBT shows promise as a therapeutic approach, particularly in improving time management skills, emotional regulation, and cognitive functioning. Further research is needed to explore the long-term efficacy and mechanisms of action of group CBT in this population. Overall, research studies on the conceptualisations of the phenomena are still in progress through the development of various measures of assessment, theoretical models, and methodologies. Furthermore, substantial future research is warranted to assess the extent of its clinical or diagnostic or clinical validity and efficacy of various psychotherapy models on BAs. In conclusion we can say that addictive problems are not just confined to chemical ingestion behaviours and that the current review do support the concept that most if the repetitive excessive activities or behaviours of reward seeking nature of do have many similarities with the characteristics of SUDs.

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Review

Beyond Snoring: Understanding Obstructive Sleep Apnea

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ABSTRACT

Obstructive Sleep Apnea (OSA) is a common sleep disorder marked by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to sleep disruption and significant reductions in blood oxygen saturation. Epidemiological data show that OSA affects a substantial portion of the adult population, with higher prevalence in males and individuals with obesity. The pathophysiology of OSA involves intricate interactions between anatomical and neuromuscular factors contributing to airway collapse, with key risk factors including obesity, craniofacial abnormalities, and genetic predispositions. Clinically, OSA manifests through symptoms such as loud snoring, witnessed apneas, excessive daytime sleepiness, and cognitive impairments. Diagnosis typically involves polysomnography or home sleep apnea testing to confirm the presence and severity of the disorder. Treatment strategies are varied, encompassing lifestyle modifications, continuous positive airway pressure (CPAP) therapy, oral appliances, and surgical interventions. Effective management of OSA is vital to reduce associated health risks, including cardiovascular disease, hypertension, and metabolic disorders.

KEYWORDS: Obstructive Sleep Apnea, Snoring, Sleep disorders, Airway Obstruction

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse of the pharyngeal airway during sleep. While individuals typically breathe normally when awake, they struggle to maintain airway patency during sleep. It is alsoassociated with increased morbidity and mortality and diminished quality of life[1]. The airway often collapses behind the uvula, soft palate, or tongue. This collapse usually results in arousal from sleep, though not always. These respiratory pauses lead to hypoxia and hypercapnia, causing cycles of apnea, hyperpnea, and intermittent hypoxia and hypercapnia throughout the night.

The complexity of OSA is exemplified by its multifactorial etiology. Such etiologies involve the craniofacial structures, neuromuscular tone, and other related factors. Collapsibility of the upper airway is influenced further by hormonal fluctuation (e.g., pregnancy or menopause), obesity, rostral fluid shifts, and genetic predisposition that influence craniofacial anatomy. OSA severity is heterogeneous among patients with the disorder[2].

Patients with OSA often report loud snoring, witnessed gasping, choking, or apnea, and excessive daytime sleepiness. Apnoeas (breathing cessation for 10 seconds or longer) and hypopneas (marked reduction in tidal volume) are common during sleep. Morning headaches, sexual dysfunction, and depression may prompt a referral to a sleep lab for an overnight study. Various parameters are monitored, including sleep patterns, respiration, oxygen saturation, EKG, and leg EMG.

A hypopnea is scored only if it results in a 3-4% decrease in arterial oxygen saturation or causes an arousal from sleep. Risk factors for OSA include obesity, increased neck circumference, craniofacial abnormalities, hypothyroidism, and acromegaly. Differential diagnosis includes simple snoring, central sleep apnea, and other causes of daytime sleepiness such as insufficient sleep, circadian rhythm disorders, narcolepsy, and periodic limb movement disorder. Polysomnography is the standard diagnostic test, though it requires significant technical expertise and is labor-intensive and time-consuming.

Epidemiology

Obstructive sleep apnea (OSA), defined by an apnea-hypopnea index (AHI) greater than 15, affects 2% to 14% of adults, with prevalence varying by gender and ethnicity and potentially higher rates in African Americans. When symptoms are not considered, 24% of men and 9% of women have an AHI over 5. Current estimates suggest that 20% of adults have mild OSA (AHI 5-15) and 6% to 7% have moderate to severe OSA (AHI > 15)[3], making it a common disorder. OSA is often insidious, with patients unaware of symptoms like loud snoring, breathing pauses during sleep, poor sleep quality, and excessive daytime sleepiness. Early recognition and treatment can improve neurobehavioral and cardiovascular outcomes.

The occurrence of OSA is strongly associated with body mass index (BMI) and central obesity, with 41% to 58% of OSA cases directly attributable to obesity. Weight loss consistently reduces AHI. OSA prevalence is high in the elderly, suggesting a link to sleep-related mortality, though nightly snoring decreases after age 65. Smoking is also linked to snoring and OSA, potentially due to airway inflammation and sleep instability from nicotine withdrawal. Passive smoking increases habitual snoring risk by 1.6 times.

Population-based studies suggest that OSA prevalence is as high or higher in African-Americans compared with Caucasians. An AHI of 30 or higher was 2.5 times greater in African-Americans relative to Caucasians, controlling for BMI and other confounding factors. The prevalence of OSA (adjusted for BMI and other potentially confounding factors) was higher in African Americans than in Caucasians. Western nations are provocative because obesity, a strong risk factor for OSA, is prevalent in white populations, but is relatively uncommon in Asian countries[3].

Pathophysiology

The human upper airway is a unique multipurpose structure involved in performing functional tasks such as speech, swallowing of food/liquids, and the passage of air for breathing. The anatomy and neural control of the upper airway have evolved to enable these various functions. The airway, therefore, is composed of numerous muscles and soft tissue but lacks rigid or bony support[4].

The human upper airway is a complex structure that extends from the external nares to the epiglottis. In patients with obstructive sleep apnea (OSA), the main site of airway collapse can range from the back of the nasal septum or choanae to the epiglottis, with most collapses occurring behind the uvula/soft palate or the tongue. The primary components of the upper airway include the nose, nasopharynx, retropalatal oropharynx, retroglossal oropharynx, hypopharynx, and larynx.

In normal individuals, the nose provides the greatest resistance in the airway, primarily at the nasal valve. The lateral walls of the nose consist of the inferior, middle, and superior turbinates (conchae), while the medial wall is the nasal septum. Although the nose adds considerable resistance to inspiratory airflow, it does not collapse in OSA due to its supportive cartilaginous structure, which is minimally dependent on muscle activity. Consequently, nasal resistance is not significantly affected by sleep. However, increased nasal resistance can create more negative intrapharyngeal pressure, potentially contributing to pharyngeal collapse at other sites.

The nasopharynx extends from the end of the nasal turbinates to the hard palate and generally does not contribute to pharyngeal collapse. The oropharynx, running from the hard palate to the epiglottis, is often divided into the retropalatal and retroglossal components, separated by the caudal end of the soft palate. The anterior wall of the oropharynx comprises the soft palate and tongue, while the posterior wall includes the superior, middle, and inferior constrictor muscles. The lateral pharyngeal walls are primarily muscular, including the constrictors, palatoglossus, palatopharyngeus, styloglossus, stylohyoid, stylopharyngeus, and hyoglossus muscles. Lymphoid tissue may also be present.

In most normal individuals, the oropharynx remains open without muscle activity. However, the muscles surrounding this part of the airway can significantly influence its shape and size. As the oropharynx is the primary site of airway collapse in OSA patients, controlling the muscles that form the airway walls is crucial in the pathogenesis of sleep apnea. The hypopharynx, extending from the base of the epiglottis to the larynx and esophageal opening, like the nasopharynx, is not commonly a site of collapse in OSA patients.

A substantial number of muscles control the pharyngeal airway, facilitating its primary functions of breathing, speech, and swallowing. These muscles are categorized into four major groups:

1. Muscles controlling tongue position and shape.
2. Muscles controlling palatal shape and position.
3. Muscles influencing hyoid bone position.
4. Pharyngeal constrictor muscles.

Although numerous intrinsic muscles in the tongue dictate its protrusion and shape and may not be directly involved in respiratory function or maintaining airway patency, studies on anesthetized rats show that intrinsic tongue muscles can exhibit respiratory modulation under hypercapnic and mildly hypoxic conditions.

The great majority of people with sleep apnea possess ventilatory control systems that are capable of precise regulation of their alveolar ventilation and arterial blood gases with extremely small variations from the norm throughout the waking hours. In addition, these healthy control systems, while awake, possess sufficiently sensitive feedback and feedforward controls to ensure precise coordination of chest wall and upper airway "respiratory" muscle recruitment so as to provide maximum airway diameter, low airway resistance and optimum lung volumes and respiratory muscle lengths, regardless of the ventilatory requirement[5].

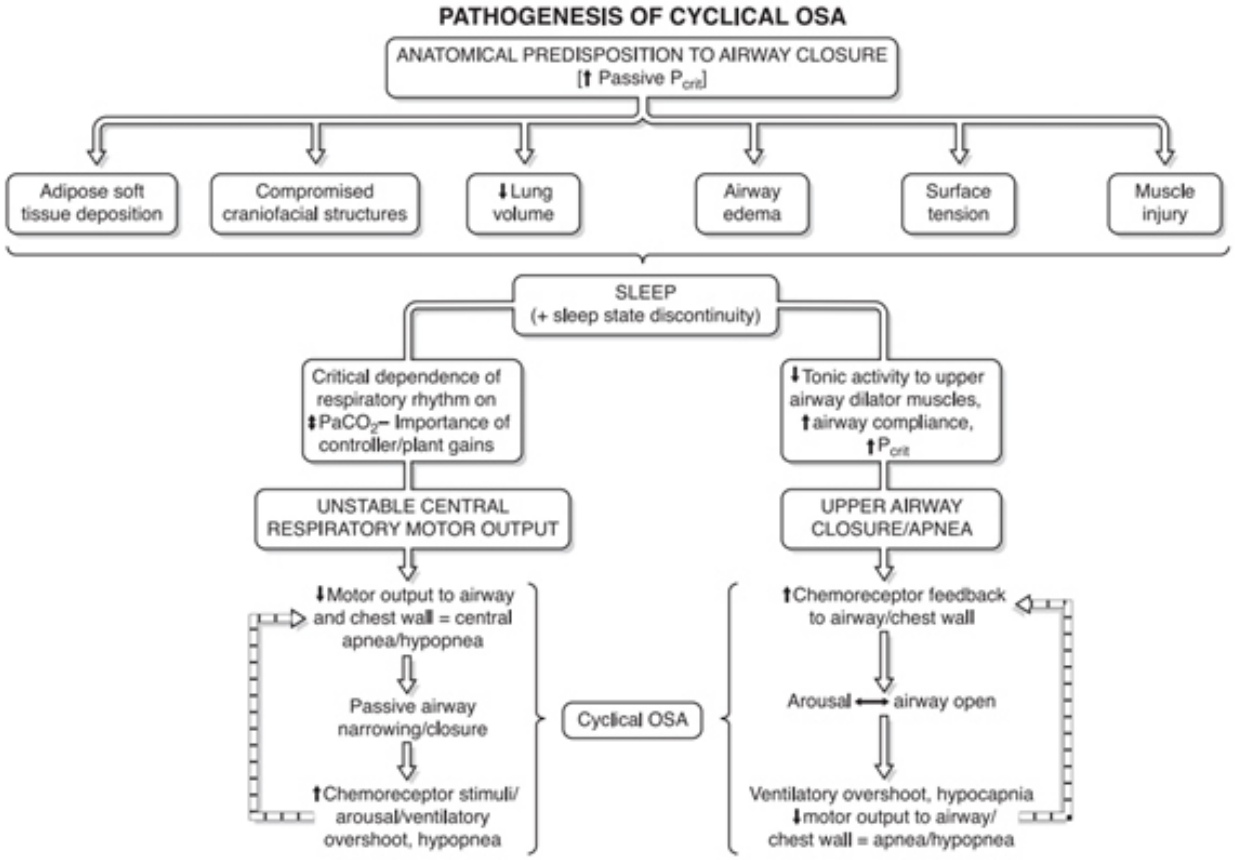

Figure 1: Map for the Discussion of Pathogenesis of Cyclical Obstructive Sleep Apnea[5]

Clinical Presentation

Individuals with obstructive sleep apnea (OSA) often seek medical attention due to symptoms like excessive daytime sleepiness (EDS), loud snoring, or witnessed apnea during sleep. EDS is defined as an inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep. This symptom is prevalent, affecting over 30% of the U.S. population, and can significantly interfere with daily activities such as work, childcare, and driving. Evaluating patients with suspected OSA involves a detailed history and physical examination.

History Taking

Because many patients report Excessive daytime sleepiness, it is crucial to assess its presence and severity. 30–50% of the general population without Obstructive sleep apnea syndrome report moderate to severe sleepiness[6]. Subjective scales like the Epworth Sleepiness Scale can help quantify the level of daytime sleepiness. Additionally, clinicians should ask about specific instances where sleepiness affects activities such as driving, work, or social interactions. Patients often underestimate the severity of their EDS due to its chronic nature, making it challenging for them to recognize normal daytime alertness.

Physical Examination

A thorough physical examination is essential in evaluating possible OSA. Key indicators include an elevated body mass index (BMI) and obesity, which increase the risk of OSA due to additional fatty tissue in the oropharyngeal structures, including the tongue. Measuring neck circumference is also important, as a circumference greater than 17 inches in men and 16 inches in women is a significant risk factor for OSA.

Tests for sleep disordered breathing Full polysomnography (PSG) are traditionally regarded as the gold standard for the diagnosis of OSAHS. Typically, it requires admission to hospital with a trained technician present throughout the night.

Monitoring of Respiration

The diagnosis of SDB rests upon detecting changes in oronasal airflow and respiratory effort to define apnoeas and hypopnoeas. However, increased work of breathing usually, but not always, associated with loud snoring alone can lead to sleep disruption and daytime symptoms[6].

The Mallampati classification[7] is useful for assessing airway visibility and correlates with OSA risk. The classification involves having the patient sit, open their mouth, and fully protrude their tongue without phonation:

- **Class I:** Soft palate, hard palate, uvula, and tonsillar pillars are visible.
- **Class II:** Soft palate, hard palate, and uvula are visible, but not the tonsillar pillars.
- **Class III:** Only the soft and hard palate and the base of the uvula are visible.
- **Class IV:** Only the hard palate is visible, indicating a crowded airway and a high risk for OSA.

Checking the extremities for clubbing or cyanosis can help identify underlying cardiovascular or pulmonary diseases. A detailed neurological examination, focusing on cranial nerves and motor function, is also crucial. Significant motor weakness or signs of central nervous system injury may indicate a risk for more complex sleep-disordered breathing, such as sleep-related hypoventilation or central sleep apnea, requiring more comprehensive evaluation and treatment.

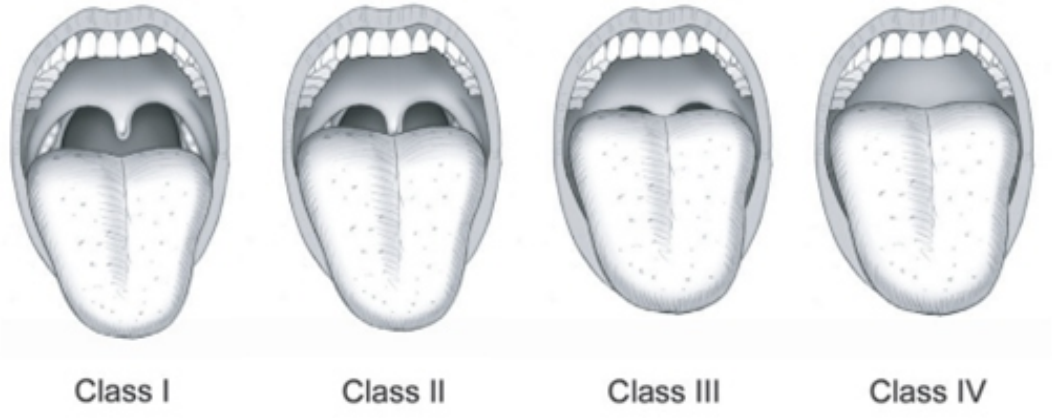

Figure 2: Mallampati Airway Classification (I-IV Scale).

During assessment, the patient is instructed to open his or her mouth as wide as possible, while protruding the tongue as far as possible[7]

Overall, a combination of thorough history taking and a detailed physical examination is essential for the effective evaluation and diagnosis of obstructive sleep apnea.

Risk Factors

Obesity and OSA: Excess weight is the strongest risk factor for OSA. Studies show a graded increase in OSA prevalence with increasing BMI. Even a small increase in BMI is associated with a higher risk of OSA. Weight loss, either through surgery or diet, can significantly reduce OSA severity. The distribution of body fat, especially around the upper body and neck (android obesity), is particularly linked to OSA risk[8].

Soft Tissues and Skeletal Features: Craniofacial abnormalities, like a small or retruded mandible and maxilla, can contribute to OSA. The position of the hyoid bone and tongue size and position also play a role. Thickening of soft tissues in the throat, like the tonsils, soft palate, and uvula, can narrow the airway and increase OSA risk. Craniofacial characteristics associated with OSA include aspects of skeletal morphology pertaining to the mandible, maxilla, cranial base, hyoid and head position, as well as soft tissue morphology, relating to size of upper airway soft tissues[9].

Fat Distribution: The way fat is distributed in the body can affect OSA risk. People with more fat around the neck and throat area (android obesity) are at a higher risk because this can compress the airway, making it more likely to collapse during sleep. Visceral fat has been proposed as a potential mediator of the relationship, because both OSA and insulin resistance are more closely associated with the size of visceral fat deposits than with BMI alone[10].

Upper Airway Anatomy: Structural abnormalities in the upper airway, such as a small jaw, enlarged tonsils, or a large tongue, can contribute to airway obstruction during sleep. These anatomical factors can reduce the size of the airway, making it more susceptible to collapse. enlargement of several of the upper airway soft tissue structures increases the risk for sleep apnea, the size of these structures may be correlated with each other[11].

Nasal Obstruction: Conditions that cause nasal congestion or obstruction, such as a deviated septum, swollen turbinates, or chronic nasal inflammation, can increase the resistance to airflow through the nose. This increased resistance can lead to greater negative pressure in the airway during breathing, increasing the likelihood of collapse.

Smoking and Alcohol: Both smoking and excessive alcohol consumption can contribute to airway inflammation and irritation, which can increase the risk of OSA. Smoking can also lead to the development of respiratory conditions that further compromise airway function. There are a number of detrimental respiratory effects attributed to smoking which include an accelerated loss of lung function, increased respiratory symptoms, increased rates of respiratory illness and infection, and increased rates of obstructive airway disease[12].

Specific Diseases and Conditions: Certain medical conditions, such as hypothyroidism, acromegaly, amyloidosis, and Down syndrome, are associated with an increased risk of OSA due to factors such as enlarged tissues or abnormal craniofacial structure. Neurological disorders that affect the muscles involved in breathing can also increase the risk of OSA.

Body Position: The position in which a person sleeps can influence the severity of OSA. Sleeping on the back (supine position) can worsen OSA symptoms because gravity pulls the tongue and soft tissues toward the back of the throat, increasing the risk of obstruction. In contrast, sleeping on the side can help keep the airway more open

Other Risk Factors: Certain conditions like polycystic ovarian syndrome (PCOS), stroke, and neurological disorders can also increase OSA risk. Body position during sleep, with supine posture increasing OSA episodes, is another factor to consider.

Diagnosis of Obstructive Sleep Apnea

History and Examination: The assessment of obstructive sleep apnea (OSA) begins with a detailed sleep evaluation, including a thorough history to identify symptoms of OSA and assess for other sleep disorders and related health conditions. Physical examination should include measurements such as body mass index (BMI), neck circumference, and blood pressure. A focused examination of the ear, nose, and throat is also important to check for factors that may contribute to OSA, such as nasal congestion or abnormalities in the throat and mouth.

Screening Tools: While screening questionnaires and prediction algorithms can be used to identify individuals at risk for OSA, they are not sufficient for diagnosing OSA on their own. These tools have limitations in terms of accuracy, particularly in certain populations. Therefore, they should not replace objective sleep testing, such as polysomnography (PSG), which is considered the gold standard for diagnosing OSA.

Polysomnography (PSG): PSG involves monitoring multiple physiological parameters during sleep to diagnose OSA. It is typically conducted in a sleep laboratory with trained technicians. PSG measures various parameters including brain activity (EEG), eye movements (EOG), muscle activity (EMG), airflow, chest and abdominal movements, oxygen levels in the blood, heart rate, snoring, and body position. PSG is recommended for patients with suspected OSA, especially those with certain comorbidities like heart failure or chronic obstructive pulmonary disease.

Patient Selection for PSG: While PSG is recommended for patients with certain comorbidities, its utility and validity in patients with other conditions or factors affecting testing have not been extensively studied. Therefore, PSG remains the preferred diagnostic test for OSA in these patients.

Second PSG: In cases where the initial PSG results are negative but there is a high clinical suspicion for OSA, a second PSG may be considered. Studies have shown variability in the

severity of OSA between nights, and a second PSG may detect OSA that was missed during the first test. However, the decision to undergo a second PSG should be carefully considered, weighing the potential benefits against the risks and inconveniences for the patient.

The diagnosis of OSAS is not based solely on the detection of abnormal respiratory events during sleep, but equally includes relevant clinical features[13].

Management of Obstructive Sleep Apnea

1. Non- Surgical Management

Positive Airway Pressure (PAP) Therapy: PAP therapy is the primary and most effective treatment for obstructive sleep apnea in adults[14]. Continuous positive airway pressure (CPAP) has been used since 1981 and works by maintaining the upper airway's openness during sleep. It is also effective for treating other sleep-related breathing disorders such as central sleep apnea and hypoventilation. PAP therapy comes in different forms, including CPAP, auto-titrating positive airway pressure (APAP), bilevel positive airway pressure (BPAP), and adaptive servo ventilation (ASV). CPAP machines deliver a constant pressure regardless of the person's sleep stage or position.

Guidelines for PAP Therapy: Recent guidelines from the American Academy of Sleep Medicine (AASM) recommend PAP treatment for obstructive sleep apnea based on a diagnosis established through objective testing. It is recommended for patients experiencing excessive daytime sleepiness, impaired sleep quality, and comorbid conditions like hypertension. Other guidelines suggest PAP treatment for moderate to severe obstructive sleep apnea (AHI > 15) or mild sleep apnea (AHI 5–15) with symptoms like excessive daytime sleepiness, nonrestorative sleep, insomnia, neurocognitive dysfunction, or a history of mood disorder, hypertension, or cardiovascular disease.

Mask Options: There is a range of interface or mask options available for delivering positive pressure therapy in obstructive sleep apnea (OSA). These include masks that fit into the nostrils (nasal pillows) or that cover the nose (nasal mask), are inserted into the mouth, cover both the nose and the mouth (oronasal mask or full face mask), or even the entire face (total face mask or helmet)[15].

Adherence to continuous positive airway pressure (CPAP) is a crucial aspect of therapy and the benefits of positive airway pressure (PAP) are most evident in patients who comply with treatment and have longer durations of CPAP use full facemasks are believed to exert pressure on the lower jaw, potentially causing it to move backward during sleep, reducing airway dimensions and increasing airway resistance. However, some individuals find it challenging to keep their mouth closed despite using a chin strap or are not comfortable with nasal or nasal pillow-type masks. As a result, there are various full facemask options available. Masks should not leave marks on the skin for an extended period after removal in the mornings.

Manufacturers now provide warnings that masks with magnetic clips should not be used in individuals with pacemakers, or the magnetic clip should stay at least 2 inches away from the pacemaker. Most masks are hypoallergenic, typically made of silicone material. Patients often switch masks or need time to adjust to wearing them comfortably. Some unique mask styles include cloth masks or those made with memory foam.

Figure 5: Nasal Mask[16]

1. Oral Appliance Therapy

Oral appliances (OAs) are devices used to treat obstructive sleep apnea (OSA) and snoring by advancing the position of the lower jaw (mandibular advancement) or by holding the tongue in a forward position. These devices work by enlarging the upper airway space, reducing airway collapsibility, and improving airflow during sleep. OAs are typically recommended for patients with mild to moderate OSA who prefer them over continuous positive airway pressure (CPAP) therapy or who have not responded well to CPAP.

There are two main types of OAs:

(1) Mandibular Advancement Devices (MADs): These are the most common type of OAs and are similar in appearance to sports mouthguards. MADs work by advancing the lower jaw slightly forward, which in turn moves the tongue and other soft tissues of the throat forward as well. This forward movement helps prevent the collapse of the airway during sleep. MADs are custom-made to fit the individual's mouth and are adjustable to ensure maximum effectiveness and comfort.

(2) Tongue-Retaining Devices (TRDs): TRDs work by holding the tongue in a forward position using suction. By keeping the tongue forward, TRDs help prevent it from falling back and obstructing the airway during sleep. TRDs are typically used in patients who cannot tolerate MADs or who have specific anatomical issues that make MADs less effective.

The effectiveness of OAs can vary depending on the individual and the specific characteristics of their OSA. Factors such as the degree of mandibular or tongue advancement, the severity of OSA, and the presence of other anatomical abnormalities can all impact the effectiveness of treatment. In general, OAs are most effective in patients with mild to moderate OSA and are less effective in patients with severe OSA.

While OAs are generally well-tolerated, they can have some side effects. Common side effects include jaw discomfort, excessive salivation, and dry mouth. In some cases, OAs can also cause changes in bite or tooth movement. Regular follow-up with a sleep specialist is important to monitor the effectiveness of treatment, address any side effects, and make any necessary adjustments to the device.

OAs are an effective treatment for OSA, not only improving AHI but also a variety of physiologic and behavioural outcomes[17].

Overall, OAs are a valuable treatment option for patients with mild to moderate OSA who are unable to tolerate or prefer not to use CPAP therapy. They can significantly improve symptoms and quality of life for these patients and are an important part of the treatment approach for OSA

2. Other Therapies and Emerging Options for Management Of OSA

Continuous positive airway pressure (CPAP) therapy is the primary treatment for obstructive sleep apnea (OSA), though up to 10% of patients may refuse it due to adherence challenges. Anatomical studies show that shifting from a supine to a lateral position alters the upper airway shape, potentially reducing collapse likelihood. Drug-induced sleep endoscopy reveals that this positional change improves obstruction at the tongue base and larynx but not the lateral walls, suggesting persistent issues for non-positional OSA patients.

Various strategies, like the "tennis ball technique," encourage side sleeping but suffer from poor long-term compliance due to discomfort and perceived ineffectiveness. Another option is the nasal expiratory positive airway pressure (EPAP) device, which prevents airway collapse by maintaining positive pressure during exhalation. Hypoglossal nerve stimulation, involving an implantable neurostimulator to keep the airway open, is indicated for patients unresponsive to CPAP therapy with a BMI below 32[18].

3. Surgical Management

Tonsillectomy and adenoidectomy (T&A) are common procedures, with tonsillectomy being one of the oldest surgical procedures known. Historically, tonsillectomy was performed for various indications, including recurrent acute tonsillitis, peritonsillar abscess, and obstructive sleep-disordered breathing (OSDB). However, over the years, the indications for T&A have evolved, with a shift towards performing these procedures primarily for sleep-disordered breathing, particularly obstructive sleep apnea (OSA), in both children and adults.

The decision to perform tonsillectomy and adenoidectomy (T&A) is based on a thorough assessment, including history and physical examination. In children, indications include recurrent throat infections, obstructive sleep apnea (OSA), and significant tonsil and adenoid enlargement causing airway obstruction or swallowing difficulties. In adults, indications include recurrent or chronic tonsillitis, peritonsillar abscess, suspected malignancy, and management of sleep apnea, especially in those intolerant to CPAP therapy.

Surgical techniques for T&A have evolved, including traditional scalpel removal, coblation (using radiofrequency energy for less pain and faster recovery), laser tonsillectomy, and partial tonsillectomy. Adenoidectomy is usually performed with a curette or suction diathermy, with coblation or laser as options.

T&A is generally safe and effective but comes with risks such as bleeding, infection, and anaesthesia-related complications. Patients should be fully informed of these risks and benefits.

Tracheostomy is a highly effective treatment for OSA, particularly in life-threatening cases or when other treatments fail. It carries risks like bleeding, decannulation, hypoxemia, and long-term complications like wound infections and tracheitis.

The hypoglossal nerve stimulator (HNS), approved by the FDA in 2014, is an implantable device that stimulates the hypoglossal nerve to keep the airway open during sleep. It is recommended for adults with moderate to severe sleep apnea who do not have concentric collapse of the palate.

CONFLICTS OF INTEREST: None

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Review

Reactive Attachment and Disinhibited Social Engagement Disorders: A Short Review

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ABSTRACT

Attachment is a vital ingredient of social and emotional development of any child during the early stages of development. Attachment disorders are considered to be the distinct patterns of dysfunctional behaviours in social situations. Reactive attachment disorder (RAD) and Disinhibited social engagement disorder (DSED) are known as the disorders of attachment or socially aberrant problems in children those who have faced severe trauma or stress. These disorders have been described the recent version of Diagnostic and Statistical Manual of Mental Disorders (DSM) under the section entitled 'Trauma- and Stressor-Related Disorders'. The current short review highlights the conceptualization and diagnostic validity of these conditions in our practice. Furthermore it also briefly describes the available treatment options for managing these disorders. Furthermore, the current review also addresses shortcomings resulting from existing phenomenology the current classificatory systems of DSM warranting future researchers to develop new approaches to understanding the etiological or psychopathological mechanisms and the psychotherapeutic interventions in order to deal with these types of conditions.

KEYWORDS: Attachment, Disinhibited social engagement disorder, Trauma, Stress

INTRODUCTION

Attachment bonds in young children are known as the crucial component in their early development and maintenance of interpersonal or social behaviour. The complementary process of neonatal signalling and maternal perceptivity to child conduct make attachment ties essential to the early conformation of social connections[1,2]. This kind of "serve and return" connection helps children acquire early capacities similar as collaborative attention[3], which is essential for language development latterly and for complementary socialising. Also, it supports the conformation of neuronal networks in the growing brain[4-6].

On the other hand, a youth who experiences abuse at an early age is more likely to witness attachment issues or unstable[7,8], chaotic connections[9,10]. There have been reports of social skill impairments, similar as shy play and common attention, delayed language development, a dropped capacity to identify verbal cues, and diffculties relating facial expressions[1 1] Maltreatment is associated with increased threat of internal health problems[12,-17], dangerous or, poorer situations of tone-regard[18,19], and advanced situations of peer conflict, victimisation, or bullying[16,11].

Our interest in these children's social capabilities stems from the fact that the opinion of maltreatment- associated complaint (DSED) is linked to certain relationship problems. According to the American Psychiatric Association's DSM- 5, the primary symptoms of experimental social anxiety complaint (DSED) include magpie benevolence and poor social boundaries, which are frequently associated with mistreatment[20].

When the DSM- 5 was released, the term "DSED" was added to the title, marking a veritably recent change. Formerly known as the disinhibited sub-type of Reactive Attachment complaint (d-RAD)[21] or Disinhibited Attachment complaint in the European fellow, ICD- 10, DSED was also known by these terms[22]. The hypothesised aetiology and lack of primary caregiver choice led to the thesis that DSED might be an attachment complaint at the time. Despite the placement of children in foster care, several substantiations showed that the core characteristics of DSED continued. The DSM- 5 named DSED, which is now distinct from Reactive Attachment complaint (DSM- 5), was created to more represent the underpinning issues with social participation[23,24,25,26].

Foster children and adolescents represent a particularly vulnerable demographic, having generally been subordinated to abuse and neglect as well as a high frequency of internal health issues. The frequency of internal problems among youth in foster care is estimated to be relatively analogous in western nations, with nearly one out of every two children or adolescents meeting the criteria for a current internal illness[27].

The incapability to establish and sustain an emotional relationship is known as attachment complaint. It has issues with attachment in terms of conduct, passions, and connections. Beforehand nonage is generally when it manifests. There are two subtypes of this condition disinhibited social engagement complaint and reactive attachment complaint. Reactive attachment complaint is characterised by a person's incapability to trust others, especially their caregiver, their incapability to express their feelings, their inviting dread or anxiety around the caregiver, and their constant state of trouble and peril perception[28]. RAD complaint is the antipode of disinhibited social engagement complaint. It's defined as an inordinate and unhappy desire for comfort and affection from non-natives, a lack of mindfulness of limits, an inordinate desire to assuage others at the expenditure of one's own requirements, impulsive, and trouble controlling one's feelings[27,28].

DSED and RAD are the results of developing abnormal connections with important caregivers during nonage. Failure can be caused by severe early years of abuse or neglect, by being suddenly removed from caregivers between the periods of six months and three times, by having multiple caregivers, or by a caregiver not responding to a child's suggestive sweats[29].

Difference between the RAD and DSED

Children who have developed completely don't show symptoms of RAD. Little to no behaviours displayed by children with RAD indicate that they've developed organised or named attachments to anyone. While children with resistant attachments may appear to have difficulty regulating their feelings and avoidant attachments may feel to warrant comfort dogging, neither exhibits the wide lack of preference, emotional insecurity, and responsiveness associated with RAD. also, a opinion would not be made grounded only on a child's conduct in a quick, artificial laboratory setting[30]. It's possible for children with DSED to parade no attachments at each, disordered attachments, insecure attachments, or indeed secure attachments[31,32]. Though some have suggested that magpie behaviour in children who are securely attached may point to a lack of factual security, this is one of the main reasons DSED isn't considered an attachment complaint. We may be suitable to more grasp the relative significance of different behavioural patterns by doing longitudinal studies of children who are securely attached and those who are not, as well as longitudinal studies of children who are insecurely attached and those who parade magpie behaviour. Although DSED is more common in kiddies with further extreme or aberrant types of attachment, including disorganised or insecure-other, attachment disordered behaviours are basically different from behaviours reported in other attachment classifications[30].

TREATMENT

Both RAD and DSED are treatable with the intervention, according to the case studies and treatment reports, but if the symptoms get worse, there may be a beginning factor or comorbidity is present[33,34]. Children in foster care or espoused from unfavourable surroundings have challenges in multiple orders[35,36], it isn't unanticipated that there's significant comorbidity between two conditions[37,38]. Also coinciding issues must be addressed in examinations and curatives in addition to the challenges related to DSED and RAD[39].

Adolescents diagnosed with DSED or RAD frequently have co-occurring psychiatric conditions and psychosocial issues. Thus, all adolescents with DSED or RAD symptoms should get a thorough internal evaluation in compliance[38,40]. Clinicians should routinely consider any co-occurring emotional and behavioural diseases in addition to associated psychosocial issues like suicidal nature, bullying behaviour, legal contraventions, sexual exertion, and substance abuse when assessing adolescents with RAD or DSED. Teenagers might not freely bring up similar issues in discussion or during a general evaluation as doing so could beget them to feel shamed

and socially inferior. Knowing about these redundant psychosocial issues, still, may have an impact on how well the adolescent's everyday struggles are understood overall and may be essential to furnishing applicable backing and treatment[40].

The significance of allowing for individual comorbidity to completely comprehend the range of internal health issues that a person may be passing and determine the applicable position of support and treatment[40]. Psychotherapy approaches for the guardian as well as the caregiver - child relationship are suggested by the criterion. There should be treatment druthers that include substantiation- grounded curatives to promote relationship functioning, similar as Child-Parent Psychotherapy, Attachment and Bio-behavioural Catch-up, and Video Interaction to Promote Positive Parenthood. Treatment/ operation options for ADHD, ASD, and other issues may be necessary in addition to these relational interventions because it has been shown that oppressed children are more likely to also have neurodevelopment issues[27].

Establishing a long- continuing relationship with a guardian who's both emotionally sensitive and available is the most important intervention for those with DSED or RAD. nonetheless, it has been demonstrated that targeted interventions that ameliorate the asked tone- regard disciplines more effectively than general or circular interventions are concentrated on global or sphere-specific tone- regard, and that these interventions may be significant internal health preventative measures in high- threat adolescents, including those with RAD or DSED[41].

CONCLUSION

In conclusion, expansive, acclimatised operation strategies are necessary for both DSED and RAD, which are complicated conditions. For better results and to support youths in forming more positive social and attachment patterns, beforehand and regular intervention is pivotal. Advanced knowledge and appreciation of these ails will ameliorate the efficacy of treatments and help impacted children and their families.

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Review

Human Papilloma Virus Related Lesions of Oral Cavity

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ABSTRACT

Human Papilloma Virus is most commonly sexually transmitted viral infection in the world. Papilloma virus is one of the oldest virus and causative agents of a group of oral lesions. Currently the incidence of HPV related oral lesions are steadily rising globally. This review gives an insight into the structure, transmission, and morphological characteristics of HPV and oral lesion related to HPV.

KEYWORDS: Human papilloma virus, HPV oral cavity, Oral condyloma, Oral lesions

HUMAN PAPILLOMA VIRUS

Human Papilloma viruses (HPVs) are a large and diverse group of epitheliotropic double-stranded DNA viruses. There are up to 225 types of HPVs divided into 5 groups (α, ß, γ, μ, and ν)[1]. Persistent HPV infection is one of the important sexual transmitted diseases (STDs) associated with more than 5% of all cancers in the world. In other words, globally more than half of all malignancies related to infection are caused by HPV[2]. HPV infection is associated with several proliferative, wart like lesions of the skin and mucosa.

Papilloma viruses are small, non-enveloped, epitheliotropic, double-stranded DNA viruses that infect mucosal and cutaneous epithelia in a wide variety of higher vertebrates in a species-specific manner and induce cellular proliferation. More than 100 types of human Papilloma viruses (HPVs) have been identified and approximately half of them infect the genital tract. Many types of HPV have been found in cervical cancers, while others are found rarely or not at all in large series of cancers, which gives rise to the nomenclature of 'high-' and 'low-risk' HPVs. These other types are associated with other anogenital and oropharyngeal cancers.

The genomes of all HPV types contain approximately eight ORFs that are all transcribed from a single DNA strand. The open reading frames (ORF) can be divided into three functional parts: the early (E) region that encodes proteins

(E1–E7) necessary for viral replication; the late (L) region that encodes the structural proteins (L1–L2) that are required for virion assembly; and a largely non-coding part that is referred to as the long control region (LCR), which contains *cis* elements that are necessary for the replication and transcription of viral DNA [Figure 1][3].

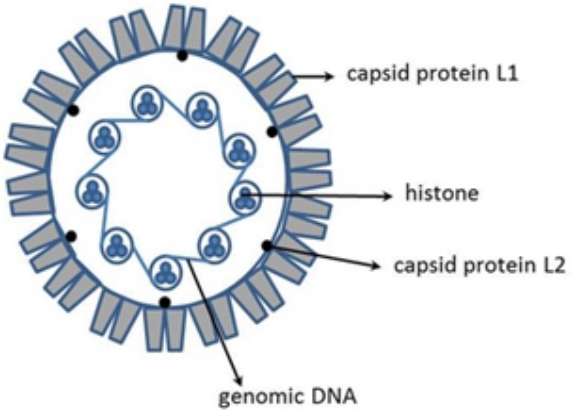

Figure 1: Structure of Human Papilloma Virus

Papilloma viruses are highly epitheliotropic; specifically, they establish productive infections only within stratified epithelia of the skin, the anogenital tract and the oral cavity[4].

The life cycle is thought to be initiated by the infection of basal epithelial cells, presumably at sites of injury. Although several potential receptors have been reported, it is unclear which of them is of physiological importance. Basal cells comprise the proliferating cellular component of stratified epithelia, in which the viral genome is established when a low copy number, nuclear plasmid and early genes are expressed preferentially although at low levels.

The viruses enter the epithelium through micro lesions and infect the basal epithelial cells where they maintain a copy number of 50–100 genomes per cell. Upon cell division, one daughter cell will remain part of the basal epithelium, while the other daughter cell will migrate up to the next level and start to differentiate. At this stage the viral DNA will segregate with the two daughter cells and replicate to maintain the 50–100 copies per cell. Virus can show productive and latent infection phase. In productive cycle the HPV have to reach cells from the basal layer of epithelium and allows keratinocytes to proliferate and express the replication of DNA, providing an environment for initial viral genome replication.

Viral latency is characterized by cessation production of new virus particles, without eradication of virus from the body. It is a complication of HPV infection in which HPV DNA can remain latent within the cells even though others have entered the productive cycle.

The transmission of HPV can occur through various ways across various mucosal sites which include sexual transmission (orogenital sex, deep kissing, and prolonged tongue to tongue contact), autoinoculation, perinatal transmission and indirect transmission through contact with hands. It can be extra genital to extra genital, extra genital to genital, genital to genital or genital to extra genital.

ORAL LESIONS

Verruca Vulgaris (VV)

VV, or the common wart, is the main presentation of cutaneous HPV infection and accounts for 70% of warts. An estimated 10% of children and young adults are affected, with peak incidence occurring in teenagers ages 12–16. VV may be found anywhere on the skin, but is most common on the periungal region of the hands. While common on the skin, VV is relatively uncommon intraorally.

Clinically, the mucosal lesions appear similarly to their cutaneous counterparts. The labial mucosa and palate are the most common intraoral sites. The lesions are pink to white, sessile, usually less than one centimeter, and display exophytic fronds [Figure 2]. Seldom, a few VV may occur simultaneously or in clusters, representing multiple sites of infection, but solitary lesions are typical[8] caused by HPV 2 and 4. Treatment depends on location, type, and size which include cryotherapy, electrocautrization, curettage, laser ablation keratolytic agents.

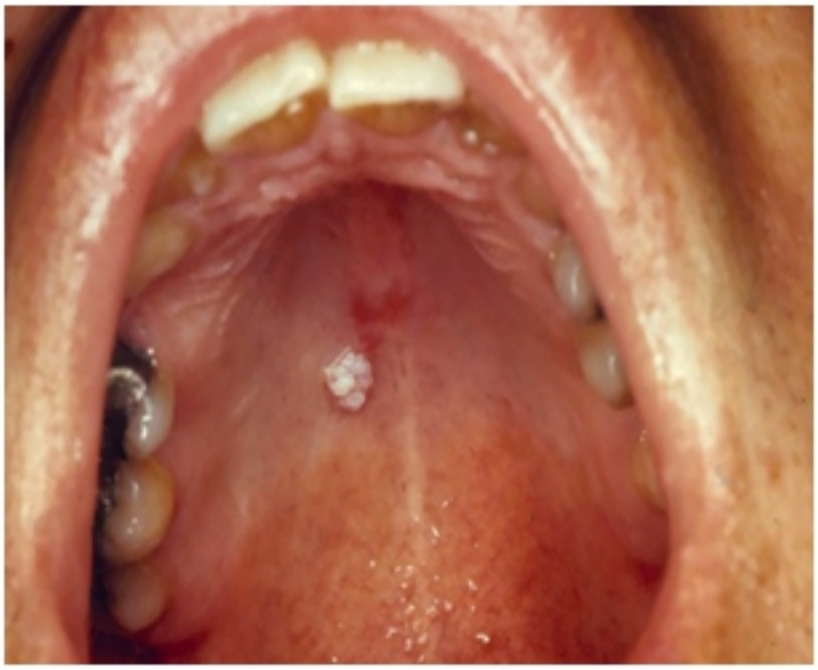

Figure 2: Lesion of Verruca Vulgaris
(Image Courtesy: Dr. Duane Schafer)

Squamous Papilloma (SP)

SP is a common lesion and the most frequent benign oral epithelial entity in both children and adults. In a large study of consecutive oral examinations of Army inductees, SP was the second most commonly encountered pathologic entity overall. Adults experience the highest incidence, with increases between the third and seventh decades. The palate and tongue are most commonly affected, but any site may be involved.

Clinically, SP is characterized by exophytic projections described as "finger-like", "Cauliflower" or "warty" are also common surface descriptors [Figure 3]. SPs are usually pedunculated, with color ranging from white to pink/red. The lesions are rarely larger than 5 millimeters in greatest dimension and usually solitary[9,10], caused by HPV 6 and 11. Treatment includes complete surgical excision of the base of lesion, along with a small area of surrounding tissue to prevent its recurrence.

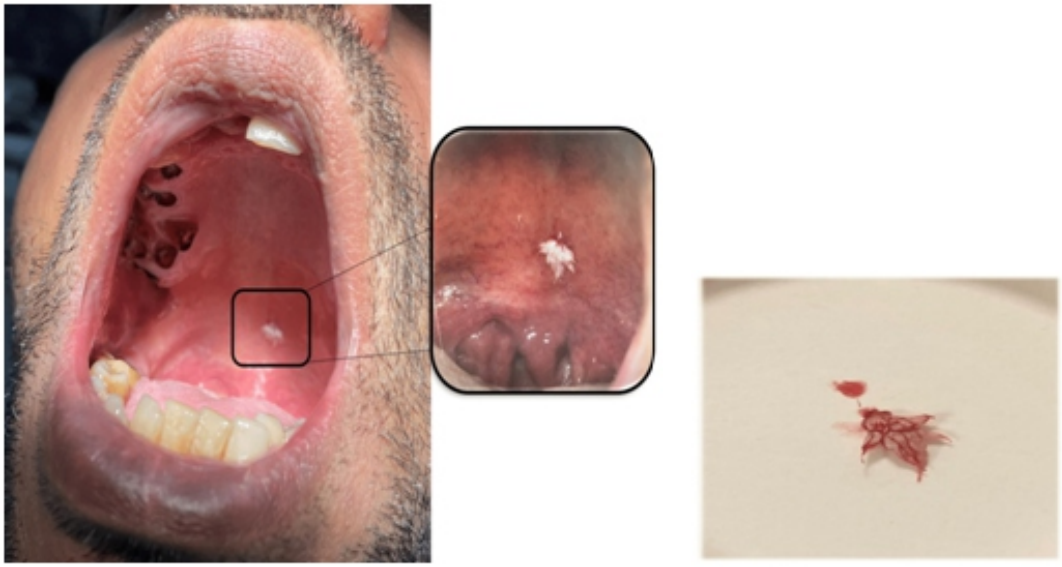

Figure 3: Squamous Papilloma

Condyloma Acuminatum

Condyloma accuminatum is a sexually transmitted HPV-related squamo-proliferative lesion occurring predominantly in an anogenital location. Oral lesions are transmitted through orogenital sexual contact.

Condyloma accuminata are larger than squamous cell papillomas and present as multiple broad based, cauliflower-like lesions with blunt processes frequently larger than 1cm [Figure 4]. The most common intraoral sites of involvement include the labial mucosa, lingual frenum and soft palate.

HPV subtypes 6 or 11 are aetiologically implicated, although high-risk subtypes may also be involved. Oral condyloma accuminata can be treated with cryotherapy or surgical excision[7].

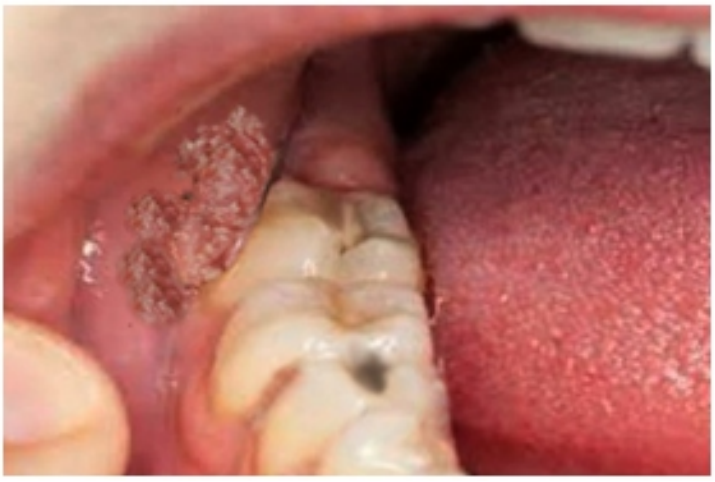

Figure 4: Oral Condyloma
(Image Courtesy: S Bhimji)

Multifocal Epithelial Hyperplasia (Heck's Disease)

Focal epithelial hyperplasia (FEH), or Heck's disease, is a rare disease of the oral mucosa; it is mostly found in children or young adults who are immune-suppressed and who live in regions with low socioeconomic status. It is characterized by asymptomatic papules on the oral mucosa, gingiva, tongue, and lips.

Multifocal Epithelial Hyperplasia presents as multiple mucosal coloured nodules measuring 2-10mm in size with a characteristic cobblestone appearance [Figure 5][5]. The lesions are predominantly present on the lips and gingivae, but can be identified at all oral mucosal sites. HPV types 13 and 32 are the usual causative agents in MEH. Lesions are clinically recognisable and resolve spontaneously within a few-months, obviating the need for treatment. Surgical or medical therapy is only indicated for large lesions which have caused functional and/or severe aesthetic complications[7,11].

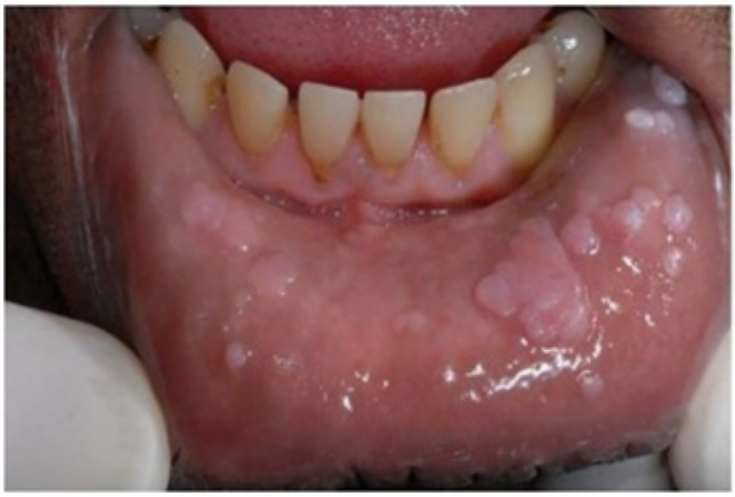

Figure 5: Multifocal Epithelial Hyperplasia

Oropharyngeal Carcinoma (OPCs)

The oropharynx consists of the palatine tonsils, base of tongue and soft palate. Most HPV-associated OPCs develop in the palatine tonsillar area. The tumours are characterised by early cervical lymph node metastases, which are frequently cystic in nature and may be the only clinical feature at the time of presentation. HPV-associated OPCs have a characteristic non-keratinising histological appearance.

HPV infection leads to transformation of oral epithelium by altering the tumor suppressor pathway and targeting the p53 and pRb genes leading to carcinogenetic changes.

Clinically, HPV-associated tumors can appear as a strawberry-like exophytic lesion, frequently at the base of the tongue or in the tonsil area. Most show poorly differentiated pathologic findings and cystic changes in the metastatic neck lymph nodes. As described, the transformation of normal oral mucosa in OSCC could be related to precancerous lesions, such as oral leukoplakia (OL), oral erythroplakia (OE), oral lichen planus (OLP), nicotine stomatitis, tobacco pouch keratosis, and oral submucous fibrosis. The role of HPV in malignant transformation of precancerous lesions has not been confirmed.

PREVENTION AND TREATMENT

The management of HPV infection depends on the type and severity of the infection. For the precancerous stage of HVP infections, include strategies as excision, ablation and immunotherapy. The gold standard is various excisional procedures of the transformation zone where the extent of excision depends on the lesion size.

In case of oropharyngeal squamous cell carcinoma, cisplatin – based chemotherapy has been the primary therapeutic approach. Radiotherapy or surgical intervention is the choice of treatment during the primary early stage.

HPV Vaccines

There are two types of vaccines against HPV: prophylactic and therapeutic HPV vaccines.

The commercial prophylactic HPV vaccines use HPV VLP to generate neutralizing antibodies against HPV major capsid protein L1.

Therapeutic HPV vaccines can eliminate preexisting lesions and infections by generating cellular immunity against HPV infected cells. HPV E6 and E7 oncoproteins are ideal targets for therapeutic intervention. Both proteins are constitutively expressed in all levels of the epithelium of HPV infected cells and play a crucial role in the induction and maintenance of HPV associated cancer[14].

CONCLUSION

Human Papilloma Virus is common and highly contagious virus showing various health hazards. There are over two hundred types of HPV and infections by many strains can resolve on their own. But it is also the initiating factor behind various epithelial lesions and cancers like cervical/ anogenital/ oral/ laryngeal/ lungs. Early detection and treatment can significantly improvise the outcomes of the diseases, vaccination and screening tests are the useful tools for the same. By understanding and spreading the awareness related to potential risk and complication of the infection we can protect the impact of HPV worldwide.

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Review

Erectile Dysfunction in Type 2 Diabetes – A Short Review

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ABSTRACT

Erectile dysfunction (ED) is a problem of getting or keeping an erection hard enough to achieve satisfactory sexual performance. The global prevalence of ED is 3–76.5%. ED constitutes a large burden on society given its high prevalence and impact on quality of life. Diabetes is a common cause of organic ED. Prevalence of ED in diabetes rate range from 35 % to 85% depending on the study, versus 26% in general population. ED occurs 10-15 years earlier in men with diabetes than it does in sex-matched counterparts without diabetes. The pathophysiology of diabetes-induced erectile dysfunction is multi-factorial. It is related to age, duration of diabetes, body mass index and diabetic complications.

KEYWORDS: Erectile dysfunction, impotence, sexual inadequacy, BM

INTRODUCTION

Erectile dysfunction (ED) also referred to as "impotence," is a problem of not getting or keeping an erection hard enough for satisfactory sexual performance. It is defined as the persistent inability to achieve and/or maintain penile erection sufficient for satisfactory sexual performance[1].

Age is a strong determinant of occurrence of ED and epidemiological studies indicate a strong relationship between ED and advancing age. While men aged 50–59 years have a 3.6 times higher risk of developing ED as compared to those aged 18–29 years, the risk is even higher (6–7 times) among males older than 70 years[2].

The causes of ED are numerous but generally fall into two categories: organic or psychogenic. The organic causes can be subdivided into five categories: vascular, traumatic/ postsurgical, neurological, endocrinologic and drug-induced[3].

Diabetes is a common cause of organic ED. Both vascular and neurologic mechanisms are implicated for ED in people with diabetes. Vascular includes atherosclerosis of penile and pudendal arteries leading to decreased blood supply to corpus cavernosum and neurological mechanisms involves autonomic neuropathy.

Studies of ED suggest that its prevalence in men with diabetes ranges from 35–75% versus 26% in general population and the onset of ED occurs 10–15 years earlier in

men with diabetes than it does in sex- matched counterparts without diabetes[3].

The wide variation in the prevalence of disease is due to use of different definitions in different populations, different diagnostic tools and varied study designs. Precise percentages are difficult to estimate because many men fail to seek help from a doctor about this problem because of embarrassment and being a taboo topic among society. Thus, despite ample evidence that ED is among the major complications in Diabetes mellitus in men, its presence remains poorly evaluated in the routine clinical practice[3].

Diabetic men are likely to have comorbidities like hypertension, obesity, metabolic syndrome, atherogenic dyslipidaemia, coronary artery diseases, etc. and each of them could be an independent risk factor in pathogenesis of ED.

The mechanisms involved in the various diseases that lead to erectile disorder include general endothelial dysfunction or dysfunction of the penile endothelium specifically, atherosclerosis, dysregulation of nitric oxide synthase, decrease of nitric oxide, low testosterone levels due to hyperprolactinemia-influenced changes in the hypothalamic–pituitary axis, vasculopathy, autonomic neuropathy, and disruption of neural proerectile processes[4]. The literature reveals that emergence and severity of ED are related with markers and mediators of inflammation and endothelial dysfunction. However, no specific marker has been identified so far that could identify this[5].

Diabetic neuropathy can similarly cause autonomic and somatic neural disorders which are of importance for erection. Besides diabetes can bring about disorders in relaxation of cavernous smooth muscles as a result of the nitric acid produced from endothelium, which may be a side effect of glycated products[2,3].

Recent evidence indicates that men with diabetes may be in growing danger of reduction of testosterone levels (hypogonadism) in addition to problems related to arteries and nerves supporting the penis[4,5]. Although an exact mechanism of this effect has not been completely identified, hypogonadism in such men may indirectly mitigate levels of pituitary hormones, responsible for stimulating testosterone production in testicles[6]. Low levels of testosterone may also lead to loss of sex drive or cause ED either directly or indirectly[7].

Proper sexual functioning is one of the most important components of quality of life[8]. The presence of ED is associated with grave psychosocial and clinical consequences including poor quality of life and depression[9]. However, it should be noted that ED is the most treatable complication of diabetes; over 95% of cases can be successfully treated[10].

The prevalence rates of sex drive, orgasmic disorders, and ejaculation problems have not been exactly determined. ED occurs in a considerable number of diabetic men, and its incidence estimation is very high in different studies, ranging from 20 to 71%. ED significantly affects quality of life in men with diabetes[11].

The magnitude of erectile dysfunction is usually underestimated in many developing countries because of several reasons. Firstly, ED is not a life- threatening condition, thus not reported. Secondly, it is associated with stigma attached to the problem, men with the problem rarely seeking help. There is also the problem of early detection and management of factors responsible for the development of erectile dysfunction[12].

Erectile Dysfunction (ED)

ED is defined as the persistent inability to achieve or maintain penile erection for successful sexual intercourse causing decreased quality of life in men[13,14]. ED is detected by having male patients' complete standardized questionnaires investigating their sexual function. One of the most practical questionnaires that is administered is the International Index of Erectile Function (IIEF)[5,] which consists of items 5, 15, 4, 2 and 7 from the full scale IIEF 15; a sum score of 21 or less indicates the presence of ED[15].

Epidemiology of Diabetic Erectile Dysfunction

The overall prevalence of ED has been reported to be 16%–25% in the general population depending on the cohort of study and the definition of ED being applied[16].The prevalence of ED in diabetes has been reported to be 60%–80% in many studies. Age is a strong determinant of occurrence of ED and epidemiological studies indicate a strong relationship between ED and advancing age. While men aged 50–59 years have a 3.6 times higher risk of developing ED as compared to those aged 18–29 years, the risk is even higher (6–7 times) among males older than 70 years[3]. Age related hormonal, metabolic and inflammatory, as well as increased prevalence of other risk factors for ED in the older population may be responsible for increased prevalence. When ED occurs in younger males, it is associated with a greater increase in the risk of future cardiac events as compared to its first detection in older males[17]. Therefore, younger men with early onset ED may be the ideal candidates for intensive CV risk factor screening and medical interventions.

Etiology of Erectile Dysfunction in Diabetes

The causes of ED are numerous but fall into two major categories: organic and psychogenic ED in diabetic men is primarily one of organic origin rather than psychogenic. ED occurs insidiously and is progressive. It is not always a late complication of the disease but can occur at any time. The organic causes fall into four principle categories: neurogenic, vascular, endocrinologic, and drug induced [Table 1].

Table 1: Etiology of Erectile Dysfunction in Diabetes

Organic
-Neurogenic
Peripheral/autonomic neuropathy
-Vascular
Atherosclerotic vascular disease
Veno-occlusive dysfunction
-Endocrinologic
Adrenal insufficiency
Hypogonadism
Hyperprolactinemia
Thyroid disorders
-Drug induced
Beta-blockers
Thiazide diuretics
Mechyldopa
Clonidine
Spironolactone
Cimetidine
Flutamine
Alcohol
Methadone
Heroin
Cocaine
Psychiatric drugs
Psychogenic
Performance anxiety
Depression
Psychological stress
Chronic illness
Relationship problems

Neurogenic Impotence

Erectile dysfunction is more common in diabetic men with peripheral and autonomic neuropathy than men without. Studies have also shown that the development of impotence is associated with the appearance of neuropathy. Indirect testing has shown some correlation between ED and autonomic neuropathy. Two such examples are the presence of bladder areflexia and bladder or bowel dysfunction, which is also more common in patients with diabetes compared to age-matched potent patients[18]. Studies have also documented abnormal vascular reflexes as noted by single beat-to-beat variation in diabetic patients with impotence[19]. Intracavernosal electromyographic needles or electrodes on the surface of the penile shaft can be used in direct testing of the autonomic innervations. The recorded electrical activity identifies the neurologic abnormalities at the level of the autonomic neuron corporal smooth muscle interface. Diabetic men with impotence have potentials that are either of short duration, high amplitude, or of low amplitude[20].

Perineal electromyography, sacral latency testing, dorsal nerve somatosensory-evoked potential evaluation, and vibration perception sensitivity testing can all be used to detect neuropathy in the sensory afferent nerves from the penile skin and the motor efferent nerves to the perineal skeletal musculature. An abnormal result in these tests suggests that there may be coexistence of the autonomic neuropathy in the corpora cavernosa.

Other research has found that diabetics have diminished levels of norepinephrine and acetylcholinesterase tissue levels in the corpus cavernosum[21] and have decreased autonomic nerve-mediated relaxation of the penile smooth muscle[22]. These studies

demonstrated that the longer the duration of diabetes, the less the ability of the cholinergic nerves to synthesize acetylcholine, supporting the notion that long-standing diabetics are more likely to present with autonomic neuropathy, and therefore ED. Diabetes also impairs relaxation of the corpus cavernosum smooth muscle to nitric oxide, decreases the synthesis and activity of nitric oxide synthase, and decreases the efficacy of nitric oxide secondary to the oxidizing conditions caused by the advanced glycation end products[23].

Vasculogenic Impotence

Diabetes has been associated with corpus cavernosum smooth muscle changes, such as increased connective tissue synthesis and atrophy of smooth muscle within the corpus cavernosum bodies in humans and animal models. These structural changes are correlated with an increased incidence of veno-occlusive dysfunction and erectile failure consistent with peripheral vascular disease seen in diabetes. Diabetes is associated with intimal, medial, and luminal changes within the artery leading to atherosclerosis. Atherosclerosis can affect the penile and pudendal arteries limiting blood flow to the corpus cavernosum. Among the men with significant peripheral arterial disease, 40% to 50% complain of some degree of erectile dysfunction[24]. Diabetic men may also have other cardiovascular risk factors, such as smoking, hypertension, and hyperlipidemia that cause an increased development of atherosclerosis in the cavernous arteries. Many invasive and non invasive tests have been developed to measure cavernosal artery systolic occlusion pressure and cavernosal arterial flow in both the erect and flaccid state. It has been found that vascular pathology In ED is related to arterial inflow, penile microvasculature, lacunar space endothelium, and penile fibroelastic frame[18].

Erectile failure can also occur secondary to venous insufficiency or veno- occlusive mechanisms. Direct injury to the sinusoidal endothelium and smooth musculature limits the ability of the smooth muscle to relax within the corpora, resulting in lack of sinusoidal dilatation. Any factor affecting the fibroelastic frame and causing inability to expand the trabeculae against the tunica albuginea and compress the subtunical venules can result in incomplete venous occlusion and subsequent venous leakage and erectile failure. The combination of low arterial flow and loss of compliance of the cavernous trabeculae causing excessive outflow of lacunar blood results in decreased penile rigidity and a diminished ability to sustain an erection. Diabetic men have an abnormal diffuse pattern of venous drainage as documented by pharmacocavernosography[18].

Endocrinologic Impotence

Hormonal causes are related to ED. Hypogonadism, hyper or hypothyroidism, adrenal insufficiency, or excessive levels of adrenal corticosteroids and prolactin may all be associated with ED in a diabetic man[25].

Drug-induced Impotence

Both prescription and over-the-counter medications have been shown to be the cause of erectile problems in as many as 25% of the general population with ED[26]. Patients with diabetes also have other cardiovascular conditions and are normally on multiple medications in order to control the above problems. Antihypertensive medications such as spironolactone, thiazides, methyldopa, clonidine, and beta-blockers all cause impotence. Antihypertensive medications may cause ED by drug- specific effects or by decreasing systolic blood pressure and compounding the already low intracavernosal penile pressure.

Even non prescription medications such as antihistamines or decongestants can affect erectile function. Medications such as cimetidine and flutamine may block the peripheral androgen receptor[26]. Most psychotropic drugs can increase prolactin levels or decrease testosterone levels and cause ED. Alcohol, methadone, heroin, and cocaine can also ED.

Pathophysiology of Erectile Dysfunction in Diabetes

Diabetes causes several changes in the neuromuscular system, all of which can contribute to ED. In men with diabetes, there is good evidence that ED is due to failure of nitric oxide (NO)-induced smooth muscle relaxation due to both autonomic neuropathy endothelium dysfunction[27]. The endothelium which is the innermost single layer of our vascular bed and also considered to be the brain of the vascular system has an important role in vascular homeostasis. It has many sensors and mediators. It secretes numerous mediators such as NO, prostacyclin and endothelin that regulate vascular tone, platelet activity and coagulation factors but also influence vascular inflammation and cell migration.

Besides hyperglycaemia, hypertension, dyslipidaemia, obesity and smoking also causes endothelial dysfunction. Endothelial dysfunction is a single most predictor of atherosclerosis, coronary artery disease and stroke.

The dynamics of erection in men is 3-fold. First, it is the neurologically mediated arterial inflow, second, there is relaxation of the corpora spongiosa smooth muscles to allow the blood to flow in the penile vasculature, and finally, there is venous obstruction which allows the blood to remain in the penile vasculature and let the penis remain erect. Any disturbance in any of the above three stages can result in ED. The vascular endothelium in the penile vasculature produces Endothelial NO synthase eNOS, and the neuronal tissues produce neuronal NO synthase n NOS. Both these synthases transport, the NO in the corpora spongiosa smooth muscle and convert the Guanosine triphosphate into cyclic guanosine monophosphate (cGMP), with the help of an enzyme guanylate cyclase. This cyclic GMP relaxes the smooth muscle and allows the blood to flow in. cGMP also potentiates Protein kinase G which inhibits calcium conduction and opens up potassium ion channels which further relaxes the smooth

muscles. The cGMP soon hydrolyses into guanosine monophosphate GMP with the help of an enzyme Phosphodiestrase 5 which is present in the penile smooth muscles and the smooth muscle contracts and leads to detumescence. Hence for proper erection, one needs to have basically a good functional endothelium which produce good amount of eNOS and also nNOS, we also need NO, which we all are aware is the chemical currency which initiates the erectogenic mechanism and also reduces as we age. There should be adequate guanylate cyclase activators and stimulators, cGMP in the more bioavailable form to keep the penile smooth muscle in a relaxed state, and something to block the phosphodiesterase type 5 (PDE5) like PDE5 inhibitors to sustain the erection[28].

Rho A/Rho-Kinase pathway is the key pathway which inhibits relaxation of the penile smooth muscle vasculature. Rho-associated protein kinase (ROCK) is a kinase which induces the formation of stress fibers and focal adhesions by phosphorylating myosin light chain. Due to this phosphorylation, the actin binding of myosin II and contractility increases. Protein kinase C and ROCK are involved in regulating calcium ion intake and these calcium ions, in turn, stimulate a myosin light chain kinase forcing contraction. Hence, inhibition of these pathways will help in relaxation of the cavernous smooth muscle and produce a sustained erection.

Diabetic neuropathy is the most common diabetic complication, affecting 10%–90% of people with diabetes, depending on the diagnostic criteria and the age and duration of DM. Some studies showed an earlier development of DN in men, compared to women. Neuropathy is a very important pathogenetic factor in the development of ED. Because DN affects all levels of the neural system, disturbances could happen at all levels in the complex process of erection from the central initiation to the penis. In the literature, much more attention is paid to the vascular aspects of ED compared to the neural ones.

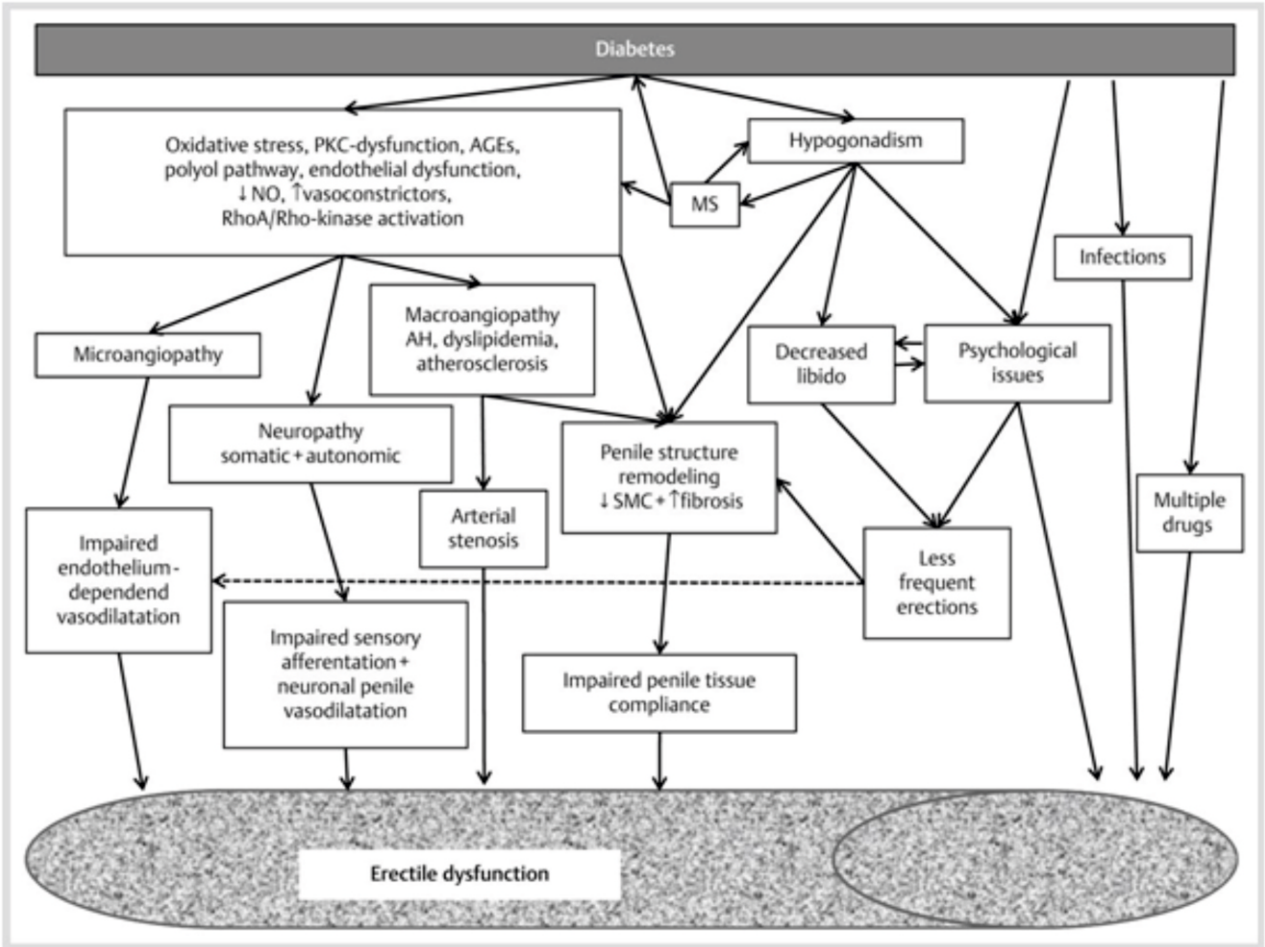

Figure 1: Pathogenesis of DED.
AGEs – advanced glucation end products; PKC – protein kinase C; NO – nitric oxide; MS – metabolic syndrome; SMS – smooth muscle cells; AH – arterial hypertension[29]

Diagnosis of Erectile Dysfunction

The diagnosis of ED starts with the patient's interview. When the anamnesis suggests the presence of ED, the administration of a validated questionnaire can be useful to objectively assess its presence and severity. In this regard, the International Index of Erectile Function (IIEF) represents a useful and validated tool[30]. In patients with DM referred for ED, the diagnostic flow-chart should include the evaluation of both TT serum levels and penile echo-color Doppler ultrasound (PCDU) examination after intracavernous injection (ICI).

According to the Endocrine Society, the diagnosis of hypogonadism can be made in the case of TT serum levels below the cut-off of 264 ng/dL (9.2 nmol/L) in at least two different measurements[31]. However, it must be considered that DM has been listed among the conditions that lower either SHBG or TT below the normal range. In these cases, the clinician has to consider that a value of free T < 64 pg/mL (220 pmol/L) confirms the presence of hypogonadism[31].

PCDU examination after ICI with prostaglandin (Pg) E1 or derivatives (e.g., alprostadil) is a second-line diagnostic test in patients with ED. Despite the lack of standardization of sampling location[32] and cut-off values, a major effort has been made over the decades to identify PCDU waveforms predicting arterial or venous ED.[33] The PCDU allows the measurement of the peak systolic velocity (PSV) and end-diastolic velocity (EDV) of the cavernous arteries in response to ICI drug administration (most often alprostadil). Both of these parameters describe the characteristics of blood flow in the cavernous arteries during erection and are currently used for the diagnosis of vasculogenic ED. Consequently, a restriction of the lumen of the cavernous artery (e.g., due to an arterial plaque or to a greater media-intima thickness) causes arterial blood flow to slow down and the PSV value decreases accordingly. In this regard, a PSV cut-off value between 25 and 35 cm/s is used as the cut-off. Conversely, in the case of dysfunction of the veno-occlusive mechanism (blood is drained too quickly from the dorsal vein of the penis), the EDV increases (>5 cm/s)[33]. In particular, a retrospective study of up to 300 patients with ED followed for 10 years reported that morphological abnormalities of the cavernous arteries (e.g., stenosis, atherosclerotic plaques, and intima-media thickness) were closely associated with cardiovascular disease. In fact, the risk for MACE was three times higher in patients with morphological abnormalities of the cavernous arteries than in those with normal morphology[34]. Once again, this evidence highlights the crucial importance of correct diagnosis and management of ED, given its consequences on cardiovascular health, especially in patients with DM.

Prevalence and Risk Factors for ED in Diabetes

In a multicentre study, the prevalence and risk factors for developing erectile dysfunction were investigated by Cho et al. in 1312 Korean men with diabetes. They used the modified International Index for Erectile Function-5 criteria to identify mild, moderate and complete ED. The mean age and median duration of diabetes were 53.8 ±6.65 and 6 years (range 1–43), respectively. The mean HbA1c and fasting glucose levels were 7.9±1.65% and 8.6 ±2.82 mmol/l, respectively. The overall prevalence of mild, moderate, complete ED and all ED (mild-to- complete) were 20.1, 19.5, 25.8 and 65.4%, respectively. ED was more common with age, reaching 79.3% in men aged > 60 years. Subjects aged > 60 years and with a duration of diabetes > 10 years were at greatest risk for all ED (OR = 10.4, 95% CI 5.8–18.5, P< 0.001) and complete ED (OR = 13.2, 95% CI 7.3–23.9, P< 0.001) when compared with the reference group (age 40–50 years with duration < 6 years). Age, duration of diabetes, HbA1c, insulin use, neuropathy and macro vascular complications were positively associated with ED, but alcohol consumption and exercise habits were negatively associated[35].

A study to determine the prevalence of and risk factors for erectile dysfunction in men newly diagnosed with type 2 diabetes mellitus (DM) was conducted by Hunayan et al.[36]. All consecutive samples of men newly diagnosed with type 2 DM attending the diabetes centre in the capital of Kuwait were included in the study. Of 323 men with newly diagnosed type 2 DM, 31% had ED; comparing potent men and men with ED, there were statistically significant differences for smoking, duration of smoking, hypertension, education level, body mass index and serum glycosylated haemoglobin level. Among these, age was the most important risk factor identified by multivariate logistic regression. Study concluded that about a third of men with newly diagnosed type 2 DM had ED; this was associated with many variables, but most notably with age at presentation[36].

A cross-sectional study was planned to assess cardiovascular risk of DM2 men with ED by Cleveringa et al. During annual check-up, the practice nurse asked 1823 DM2 men: “Do you have erection problems? Yes/ No.” ED prevalence rate was calculated. The prevalence of ED in DM2 patients was 41.3%. When categorizing by age, following prevalence was found: 40 years, 3.0%; 40–49 years, 19.2%; 50–59 years, 34.1%; 60–69 years, 45.7%; 70–79 years, 51.5%; and N80 years, 49.4%. There was no independent association between ED and HCVD [adjusted OR, 1.2 (95% CI, 0.9–1.5)]. The 10-year UKPDS CHD risk difference between men with and without ED was 5.9% (95% CI, 3.2–8.7), but after adjustment for age, this association disappeared [adjusted risk difference, 0.6% (95% CI, −1.5 to 2.7)]. The ED prevalence rate assessed by a single question was comparable to that assessed by questionnaires. ED neither did independently relate to patients' cardiovascular history nor to cardiovascular risk[37].

Awad et al. tried to explore the role of glycemic control, and its correlation to sexual function in one hundred patients with diabetes type2. The selected patients were evaluated for sexual function by asking the patients to complete the abridged form of the International Index of Erectile Function (IIEF). Results indicated that in the group with good glycemic control, the greater percentage of patients had good potency (53%), whereas a lesser percentage had fair potency (20%) and poor

potency (26%). The level of HbA1c is significantly higher with declining degrees of potency (P- value=0.003). Also, there is an association between potency degree and glycemic control (P=0.002). Study concluded that glycemic control is independently and inversely associated with ED in men with diabetes[38].

The prevalence of ED in Chinese men with type 2 diabetes mellitus was investigated by Yang et al.[39]. They also evaluated the efficacy and safety of sildenafil citrate in these patients. Patients from 42 outpatient diabetes clinics with type 2 diabetes mellitus and ED as defined by the International Index of Erectile Function (IIEF)-5 were studied. Participants with ED received three doses (100mg each) of sildenafil citrate for use over 3 months. Efficacy of sildenafil citrate was assessed using the IIEF-5 and the Global Efficacy Questionnaire (GEQ). A total of 5477 participants were evaluated, and 75.2% had ED. Age, duration of diabetes and glycosylated hemoglobin (HbA1c) 46.5% were independently and significantly associated with the presence and degree of ED. Patients who received pharmacotherapy reported significant improvements. The rate of erections as determined by the GEQ was also significantly improved following treatment. ED is a common complication in Chinese men with type 2 diabetes mellitus, and certain risk factors are associated with the presence of ED and severity[39].

A study was designed by Giugliano et al. to evaluate the prevalence and correlates of ED in a population of diabetic men[40]. Consecutive patients with type 2 diabetes were recruited among outpatients regularly attending Diabetes Clinics. A total of 555 (90.8%) of the 611 men were analyzed in this study. ED was assessed by the IIEF-5 instrument. Approximately, 6 in 10 men in their sample of diabetic men had varying degrees of erectile dysfunction: mild 9%, mild to moderate 11.2%, moderate 16.9% and severe 22.9%. The prevalence of severe ED increased with age. Higher hemoglobin A1c (HbA1c) levels were associated with ED; similarly, the presence of metabolic syndrome, hypertension, atherogenic dyslipidemia (low levels of HDL-cholesterol and high levels of triglycerides) and depression was associated with ED. Physical activity was protective of ED; men with higher levels of physical activity were 10% less likely to have ED as compared with those with the lowest level. In conclusion, among subjects with type 2 diabetes glycemic control and other metabolic covariates were associated with ED risk, whereas higher level of physical activity was protective. These results encourage the implementation of current medical guidelines that place intensive lifestyle changes as the first step of the management of type 2 diabetes[40].

A study was undertaken to find out prevalence of erectile dysfunction in Type-2 diabetic patients and its association with various risk factors. Fifty Type-2 diabetic patients fulfilling the inclusion criteria were recruited amongst outpatients regularly attending OPD of MGMCH, Jaipur. They were assessed for erectile dysfunction using International Index of Erectile Dysfunction (IIEF-5). The prevalence of erectile dysfunction in type-2 diabetics was very high (78%). Mild, moderate and severe ED was present in 6, 36 and 36% patients respectively. Prevalence of ED was found to increase with age, duration of diabetes, fasting blood sugar level, HbA1c level, hypertension and dyslipidaemia. A definite correlation between various complications and prevalence of erectile dysfunction was found[41].

A cross-sectional hospital based study was conducted among 312 diabetic patients attending diabetic clinic at Muhimbili National Hospital between May and December 2011 to determine the prevalence of ED and associated risk factors. More than half (55.1%) of the patients were found to have some form of ED (12.8%) had mild dysfunction, 11.5% moderate and 27.9% severe dysfunction). The severity of ED was correlated with increased age. Multivariate logistic regression revealed that ED was significantly predicted by old age (odds ratio (OR) = 7.1, 95% CI 1.2-40.7), evidence of peripheral neuropathy (OR) =5.9, 95% CI 1.6-21.3), and evidence of peripheral vascular disease (OR =2.5, 95% CI 1.2-5.3). Also longer duration of DM was marginally associated with ED (p=0.056). Patients with ED were also more likely to suffer other sexual domains (p<0.001). No lifestyle factor was associated with ED. The prevalence of ED was high among DM patients[13]. It was recommended that early diagnosis and detection of DM and its complications, and adherence to treatment to prevent complications should be implemented[13].

The prevalence and risk factors for ED among men with type 2 DM in a Nigerian tertiary healthcare centre was conducted by Ugwu et al.[42]. This was a cross-sectional study of 160 male type 2 DM adults, aged 30–70 years, attending a tertiary healthcare clinic. Demographic and relevant clinical information was documented. Erectile function was assessed using an abridged version of the International Index of Erectile Function (IIEF-5). 152 (95%) patients with a mean age of 60.3 ± 8.8 years completed the study. 71.1% had varying degrees of ED, while 58.3% suffered from a moderate-to-severe form. Independent predictors of ED were longer duration of DM, PAD, autonomic neuropathy, poor glycemic control, and testosterone deficiency. Study concluded that the prevalence of ED and its severe forms was high in this patient population. Poor glycemic control and testosterone deficiency were the strongest risk factors for ED, making it possibly a preventable condition[42].

Anwar et al. assessed the prevalence of ED among diabetic men and to compare the DM patients with severe ED with those having a normal erection on various sociodemographic and clinical correlates. In the study, a total of 184 diabetic patients were assessed, and 67.4% (124/184) of the participants were found to be suffering from ED and 42.4% from severe ED. those with severe ED were found to have poor glycemic control, worse lipid profile, higher body mass index, later age of onset, and longer duration of untreated diabetes as compared to non-ED patients. ED patients also scored higher on depression rating scale, had poorer general health and quality of life (QOL). Early attention to ED in diabetic patients can improve general health and QOL of the sufferers. Author

concluded that DM patients with poor glycemic control and advanced age have a higher propensity of developing severe ED, which further deteriorates the already compromised health & QOL[43].

A systematic review and meta-analysis to assess the relative prevalence of erectile dysfunction in diabetes searching major databases from inception to November 2016 for studies reporting erectile dysfunction in men with Type 1 and Type 2 diabetes mellitus was done by Kouidrat et al. They conducted a meta-analysis of the prevalence [and 95% confidence intervals (95% CIs)] of erectile dysfunction in diabetes compared with healthy controls, calculating the relative odds ratios (ORs) and 95% CIs. A random effect model was applied. From 3747 initial hits, 145 studies were included representing 88 577 men (age: 55.8±7.9 years). The prevalence of erectile dysfunction in diabetes overall was 52.5% (95% CI, 48.8 to 56.2) after adjusting for publication bias, and 37.5%, 66.3% and 57.7% in Type 1, Type 2 and both types of diabetes, respectively (P for interaction < 0.0001). The prevalence of erectile dysfunction was highest in studies using the Sexual Health Inventory for Men (82.2%, 17 studies, P for interaction < 0.0001). Studies with a higher percentage of people with hypertension moderated the results (beta = 0.03; 95% CI, 0.008 to 0.040; P = 0.003; R2 = 0.00). Compared to healthy controls (n = 5385) men with diabetes (n = 863) were at increased odds of having erectile dysfunction (OR 3.62; 95% CI, 2.53 to 5.16; P < 0.0001; I2 = 67%, k = 8). Erectile dysfunction is common in diabetes, affecting more than half of men with the condition and with prevalence odds of approximately 3.5 times more than controls. Findings suggested that screening and appropriate intervention for men with erectile dysfunction is warranted[44].

An epidemiological study of ED in men with DM in a primary health care was done by Tridiantari et al. There were 122 diabetic men who were all included in the study. The results showed that the prevalence of diabetic men with ED was 84.4%. Most men with ED had age of ≥46 years (91.0%), experienced work stress (88.5%), had low physical activity (93.1%), had obesity (88.0%) of which 86.3% had central obesity, smoking (84.6%), had DM >5 years (91.2%), and took antihypertensive drugs (90.0%). The fasting blood glucose level of respondents ≥ 126 mg/dl was 86.0% and 91.7% had sexual desire disorder. The duration of DM and aging are contributing factors of ED in males with DM, with a p-value of 0.016 and 0.013, respectively[45].

A cross sectional study was conducted from January 2016 to March 2016 by Walle et al. to assess the prevalence of erectile dysfunction and associated factors among diabetic patients. A total of 422 diabetic patients were participated with 100% response rate. The proportion of erectile dysfunction was 85.5% and it was significantly associated with higher age (AOR: 6.46, 95% CI 2.55–16.44) and Diabetic complication (AOR: 3.97, 95% CI 1.06–17.36). Therefore, screening for ED in diabetic patients, particularly for those who are in advanced age and living with DM for more than 10 years is needed for its early detection, prevention and management[46].

The prevalence and predictors of ED among diabetic patients in a tertiary hospital of Southwest Ethiopia was conducted[47]. It was a hospital-based cross-sectional study was conducted on male diabetic patients on follow-up at the diabetic clinic of Jimma Medical Center (JMC). 350 male diabetic patients were enrolled in the study. The mean (+SD) age of the study participants was 47.9 (+12.2) years. The majority, 212(60.4%) of the diabetic patients had varying degrees of ED and almost all, 207 (97.6%) of the patients were not treated for ED. Independent predictors of ED were older age and longer duration of diabetes[47].

Bahar et al.[48] conducted a study in the city of Sari in Mazandaran Province, with the aim of investigating ED in men with type II diabetes. A total number of 350 male patients suffering from type II diabetes referring to endocrinology clinics in the city of Sari. The average period of time in which the patients were facing diabetes was 3.65±5.75 years. The IIEF mean score was equal to 16.98±43.79. Erectile dysfunction (ED) was also evident in 152 patients (62.2%). Moreover, increase in age had significantly decreased the IIEF scores (p<0.001). The chance of being affected with ED among diabetic patients above 50 was 11.21 times as much as those below 50 years of age (odds ratio (OR): 11.21, 95% confidence interval (CI): 6.40-19.62). Author recommended that concerning the high prevalence rate of ED in men suffering from type II diabetes, doctors are required to directly ask them about sexual disorders in follow-up visits. Furthermore, using screening questionnaires can be helpful in identifying this problem[48].

Hospital based cross-sectional study was conducted on 362 participants in Debre Tabor Comprehensive and Specialized Hospital North West Ethiopia from August - December 2020 using systematic random sampling technique. Three hundred sixty-two diabetes patients participating in the study with the mean age being 44.4 ± 14.47 (range: 18 -78) years were interviewed. The majority (59.7%) of the diabetes patients suffered from erectile dysfunction and 13.3% were found to have severe erectile dysfunction. Bi-variable analysis showed duration of diabetes (>10 years), type of diabetes (type II), physical exercise, drinking alcohol, BMI, blood glucose, and blood pressure were associated with erectile dysfunction at 5% level ($p \leq 0.05$). Multiple logistic regression analysis revealed that duration of diabetes 10 years p = 0.001, co-existing hypertension, p = 0.002, physically inactive p = 0.003, unsafe level alcohol intake p = 0.003) and raised blood glucose p = 0.004 were independent risk factors but no association was found with other variables. Study concluded that the magnitude of erectile dysfunction in this study population was 59.7% and associated with the type of diabetes; duration of diabetic, physical exercise, alcohol drinking, increase in blood pressure, and elevated blood glucose level were independently correlated with erectile dysfunction[49].

Tamrakar et al. aimed to identify the prevalence of erectile dysfunction and its association with other risk factors among type 2 Diabetic males attending the tertiary care hospital in

Nepal. The prevalence of erectile dysfunction with varying degrees of severity was found to be 76.87% among T2 DM male patients. There was a significant negative correlation of the IIEF5 Score with the duration of T2 DM burden (r= -0.416, p<0.05) and the level of HbA1c (r= -0.391, p<0.05). There was a higher prevalence of erectile dysfunction among T2DM male patients that were also associated with poor glycemic control and the duration of T2 DM burden[50].

An institutional-based cross-sectional study was conducted involving 462 men diabetic patients at the three hospitals of the northwest Amhara region Ethopia[57]. The prevalence of sexual dysfunction was found to be 69.5% (95%CI: (65.1–73.9)). The magnitude of sexual dysfunction was prevalently observed among participants who were older (> 50 years) (AOR = 8.7, 95%CI: (3.3–23.1)). Likewise, the odds of sexual dysfunction was significantly higher among men who have lived with diabetes for a longer duration (AOR = 10.8, 95% CI: (5.3–21.9)), with poor metabolic control (AOR = 3.57, 95% CI: (1.81–7.05)), with comorbid illnesses (AOR = 5.07, 95% CI: (2.16–11.9)), and diabetic related complications (AOR = 3.01, 95% CI: 1.31–6.92). On the other hand, participants who were physically active (AOR = 0.41, 95% CI: (0.12–0.7)) and satisfied with their relationship (AOR = 0.15, 95% CI: (0.03–0.7)) showed a lesser risk of experiencing sexual dysfunction[51].

The institution-based cross-sectional study was conducted on 352 adult male diabetic patients randomly selected at Hawassa, Southern, Ethiopia. The prevalence of erectile dysfunction was 72.2% (95%CI, 1.76–3.68). After adjusting all factors, old age, diabetes duration, drinking alcohol, and poor glycemic control had shown significant association with erectile dysfunction. Author recommended that the occurrence of erectile dysfunction in this study community is very high. Drinking alcohol, poor glycemic control, age, and duration of diabetes were predictors of erectile dysfunction in this study area[52].

Dave et al. conducted a study to evaluate ED in male diabetes patients. It was a hospital-based prospective observational study. According to International Index of Erectile Function (IIEF)-5 questionnaire, patients were divided into 4 categories: mild ED with score 17 to 21, mild-to-moderate ED with score 12 to 16, moderate ED with score 8 to 11 and severe ED with score 1 to 7. Prevalence of ED in male diabetes patients was found to be 72.4%. Among 110 cases with ED, 8 had mild ED (7.2%), 27 had mild-to-moderate (24.5%), 27 had moderate ED (24.5%) and 48 had severe ED (43.6%). Prevalence of ED was found to be proportional to age. Majority of cases in ED group were those with long-standing diabetes. Correlation of ED with complication of diabetes, like nephropathy and retinopathy, was significant, whereas it was not significant with neuropathy. Significant correlation of ED was found with BMI and PLR. Author concluded that ED prevalence was high among the diabetes patients and it increased with age and duration of the disease. Presence of diabetic complications was significantly associated with ED. BMI was significantly associated with development of ED[53].

Parmar et al. aimed to determine the prevalence of ED and its predictors among diabetic men. A hospital- based cross-sectional observational study was conducted at a tertiary care centre including 357 diabetic men recruited over one and half years. ED was found in 212 (59.38%) diabetic males. A strong negative correlation was found between potency score and age (r = −0.647), and a moderate negative correlation with duration of DM (r = −0.324), systolic blood pressure (SBP), and diastolic blood pressure. BMI, fasting blood sugar, serum cholesterol, and serum creatinine showed a weak negative correlation with potency score. Serum testosterone level showed a strong positive correlation with potency score. Age, SBP, duration of diabetes, fasting blood sugar, and serum free testosterone (P < 0.05) were independent predictors of ED[54].

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Observational Study

Psychological Trauma and Associated Schemas of Sexual Assault among Female Sex Workers

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ABSTRACT

Psychological trauma is a negative human experience to an event caused by a highly stressful situation. Female sex workers are vulnerable group of people who are found to be at increased risk of being assaulted and associated psychological trauma by opposite sex people irrespective of their workplaces. However despite being a high risk population, their concerns generally remain unidentified in most of the research areas. The objective of the present study was to observe and measure the severity of sexual assault or violence and associated pre and post-traumatic schemas among female sex workers of Vadodara district of Gujarat state. A total of 30 female sex workers were selected for the study and the data was collected by direct in person interactions with these workers for the study. The data of this study is both qualitative and quantitative in nature. The severity of assault was measured by the use of Sexual Assault Severity Scale (SASS) through which assesses different criteria for sexual assault. The study findings revealed the severe level of sexual assault or violence on these workers and experienced traumatic distress leading to social isolation from the general public.

KEYWORDS: Trauma, Sexual assault, Female sex workers, High risk population, Violence

INTRODUCTION

Psychological or emotional trauma is the result of highly stressful events involving a severe threat to one's life and safety concerns. It is thought to disrupt our equilibrium system leading to a grave concern to our sense of security resulting in feeling disconnected helplessness and other emotional problems. It can cause severe emotional damage to the person leaving him or her to suffer with memory flashbacks and social isolation. With respect to female sexual workers, they often face physical violence in their workplaces and hence are more vulnerable to have

emotional trauma. From evolutionary perspective, sexuality is widely accepted as fundamental and significant aspect of human life that typically includes features of sexuality and sexual behaviour[1,2]. As a strong human drive it can be expressed to show love, to achieve pleasure and finally to fulfill the ultimate evolutionary goal of reproduction[3]. One of the fundamental motivations for human activity is the desire to have sex. The word "sex" is commonly used in everyday language and in a variety of contexts which is most frequently used to describe physical activity and biological sex[4]. The term "sexuality" in its broadest sense is frequently used to refer sexual behaviour, desire, identities, and gender differences[5,6]. Although sex is a natural process, various ideals and behavioral norms regarding acceptable sexual behavior have been formed by various religions, cultures, philosophies, and legal systems — systems concerned with influencing human behavior. Hence, all aspects of sexuality and sexual practice in any particular culture are mostly influenced by the cultural norms regarding sexual contact, patterns of behavior that regulate sexual behavior in society. Thus, sexuality is a multifaceted, complex phenomenon which covers the numerous ways that people exhibit their sexuality as well as their various sexual likes and dislikes[7]. All of them have an impact on how we explore or express our sexuality and how we view others and ourselves as sexual beings[8,9]. However, premarital sex, having several partners, and unprotected sex are just a few examples of unhealthy sexual conduct. Furthermore, such risky sexual activities can lead to unfavorable health consequences like HIV/AIDS, unintended pregnancies, and unsafe abortions[10]. According to fragments of data, adolescents who have experienced maltreatment from others and show antisocial tendencies are more likely to engage in unsafe sexual practises[11].

With respect to violence in sex, sexual assault can be defined as any physically harmful or unwanted sexual activity which is attempted through violence or coercion and committed against a person's consent. The incidents of sexual assault are generally noticed in female sex workers, especially the so-called high-class call girls, are generally found to encounter such acts of violence and discrimination[12,13]. Female sex worker can be defined as an adult woman who performs consensual sex as her primary source of income[14]. However, various studies reveal that sex workers regularly suffer from physical violence and rape at the hands of their clients[15]. Hence, in order to gain in-depth knowledge about the sexual assault among female sex workers the present study aimed at studying the Sexual assault among female sex workers in Gujarat state.

METHODOLOGY

For the purpose of the study, 42 female sex workers were approached, of which 30 provided consent for the study. The sample size thus was 30 female participants. The data was collected using Sexual Assault Severity Scale (SASS) from Vadodara and Bodeli areas of Gujarat state. Qualitative and Quantitative both research methods were used in this study. The research used the survey method via offline mode only. The SASS scale was used to assess the severity of sexual assault among female sex workers. Data was collected in an offline mode by direct interaction with sex workers at their work places and at different areas. Data was collected individually.

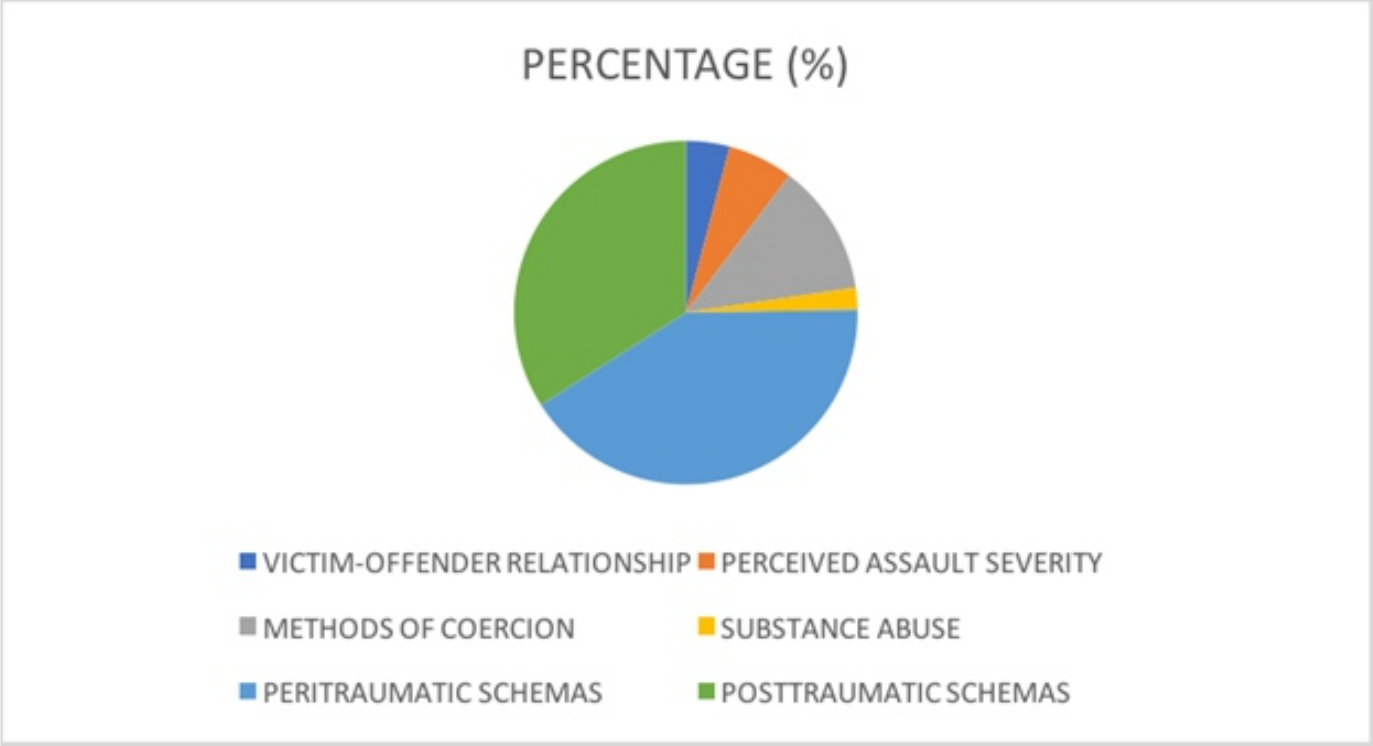
RESULTS

The aim of this study is to measure the severity of sexual assault and associated traumatic schemas among female sex workers and for those different categories of various subtopics had been measured. All quantitative data were in the form of total and percentage in the given table. The Pie-Chart represents the severity of sexual assault among female sex workers through Victim-offender relationship, Perceived assault severity, Method of coercion, Substance abuse, Peri-traumatic schemas and Posttraumatic schemas. The overall result reveals that quantitative data includes victim offender relationship with a mean SCORE 9.8 and Standard deviation 19.06 which makes the total of 4%. Perceived assault severity with a mean value 14.83 and Standard deviation 5.88 making the total of 6%. Method of coercion with a mean value 29.77 and Standard deviation 23.13 which makes the total of 12%. Substance abuse with a mean value 5.8 and Standard deviation 5.90 which makes the total of 2%. Peritraumatic schemas with a mean value 96.87 and Standard deviation 18.27 which makes the total of 40% and posttraumatic schemas with a mean value 80.47 and standard deviation 24.84 which makes the total of 33% whereas the qualitative data described sexual assault characteristics like between the age range of 18-25 years experienced more sexual assault. The qualitative analysis of the data reveals that large number of Female sex workers experienced sexual assault with one person only and other experienced more than two individuals. Sexual experiences mostly occurred in deserted areas and at someone's house or place. In Victim-offender relationship, sexual assault was mostly performed by strangers or by close friends and most of the time no one was present during the sexual assault. In the Methods of Coercion, some ways to pursue sexual act where the female sex workers were tried to convince and if they denied then they were threatened to do the sexual assault. If sex workers still denied performing the sexual act then they were held down or restrained because of which they suffered through soreness. In substance abuse, mostly sex workers were not drunk and were not using any illicit substances during sexual act but a person who wants to perform sexual act was mostly drunken and some of them consumed drugs (marijuana). The common observation was that, they trust others easily because they thought that they were weak and now they are like they will not be the same person ever again.

Table: Statistics on the severity of sexual assault among female sex workers through various means

GROUP	PERCENTAGE (%)	MEAN (M)	STANDARD DEVIATION (SD)
VICTIM-OFFENDER RELATIONSHIP	4%	9.8	19.06
PERCEIVED ASSAULT SEVERITY	6%	14.83	5.88
METHODS OF COERCION	12%	29.77	23.13
SUBSTANCE ABUSE	2%	5.8	5.90
PERITRAUMATIC SCHEMAS	40%	96.87	18.27
POSTTRAUMATIC SCHEMAS	33%	80.47	24.82

Pie Chart: Percentage of the severity of sexual assault among female sex workers through various means



CONCLUSION

The issue of violence against female sex workers and subsequent psychological or emotional trauma has periodically emerged as a pervasive major social and public-health concerns wordwide[16,17]. However, the problem has not attained much attention in assessing the severity of this assault in existing literature. Sexual violence as a traumatic event can generate the emotional distress and related traumatic schemas. A traumatic schema refers to the set of beliefs and emotions resulting in patterns of maladaptive behavior that is developed after a traumatic event. The present study reveals the presence and severity of sexual assault or violence, psychological trauma and associated pre and post-traumatic schemas among female sex workers residing in Vadodara and Bodeli areas of Gujarat state. The participants of the study experienced severe level of sexual violence, forced sex and social isolation from the general public. The qualitative analysis of the data highlights that female sex workers experienced severe levels of sexual assaults and psychological trauma through various means viz. victim-offender relationship, perceived assault severity, method of coercion, Substance abuse, peri-traumatic schemas and posttraumatic schemas by one or more perpetrators. The study findings reveal that most of the female sex workers in peri-traumatic schemas which are known as emotional distresses experienced during and/or after an assault were more associated with the development posttraumatic stress disorder (PTSD). However, in posttraumatic schemas almost similar number of other sex workers became habituated with that. In conclusion, the exploration of trauma schemas can be made accessible to the provision of any kind to mental health services. The study strongly suggests and upholds the basic human rights of these workers and proper knowledge about the work should be given to the female sex workers. Furthermore, government policies, protection laws and awareness programs for their basic rights should be implemented properly at various levels for the upliftment of female sex workers.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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New Drug Approvals

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
1.	Molluscum Contagiosum	Zelsuvmi (berdazimer sodium) Topical Gel	Ligand Pharmaceuticals Incorporated	Zelsuvmi (berdazimer sodium) is a nitric oxide-releasing agent indicated for the topical treatment of molluscum contagiosum (MC) in adults and pediatric patients 1 year of age and older.	January 5, 2024
2.	Eosinophilic Esophagitis	Eohilia (budesonide) Oral Suspension - formerly TAK-721	Takeda Pharmaceutical Company Limited	Eohilia (budesonide oral suspension) is a mucoadherent formulation of the approved corticosteroid budesonide used for the treatment of eosinophilic esophagitis.	February 9, 2024
3.	Frostbite	Aurlumyn (iloprost) Injection	Eicos Sciences Inc.	Aurlumyn (iloprost) is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations.	February 13, 2024
4.	Melanoma	Amtagvi (lifileucel) Suspension for Intravenous Infusion	Iovance Biotherapeutics, Inc.	Amtagvi (lifileucel) is a tumor-derived autologous T cell immunotherapy used for the treatment of adult patients with unresectable or metastatic melanoma.	February 16, 2024

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
5.	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	Simlandi (adalimumab-ryvk) Injection	Alvotech and Teva Pharmaceutical Industries Ltd.	Simlandi (adalimumab-ryvk) is a tumor necrosis factor (TNF) blocker interchangeable biosimilar to Humira, approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and uveitis.	February 23, 2024
6.	Urinary Tract Infection	Exblifep (cefepime and enmetazobactam) Injection	Allecra Therapeutics	Exblifep (cefepime and enmetazobactam) is a fourth generation cephalosporin and beta lactamase inhibitor combination for the treatment of complicated urinary tract infections (cUTIs).	February 22, 2024
7.	Glabellar Lines	Letybo (letibotulinumtoxinA-wlbg) Powder for Injection	Hugel, Inc.	Letybo (letibotulinumtoxinA-wlbg) is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.	February 29, 2024
8.	Osteoporosis	Jubbonti (denosumab-bbdz) Injection	Sandoz	Jubbonti (denosumab-bbdz) is a RANK ligand (RANKL) inhibitor interchangeable biosimilar to Prolia (denosumab) used in the treatment of osteoporosis.	March 5, 2024

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
09.	Osteolytic Bone Lesions of Multiple Myeloma, Osteolytic Bone Metastases of Solid Tumors, Giant Cell Tumor of Bone, Hypercalcemia of Malignancy	Wyost (denosumab-bbdz) Injection	Sandoz	Wyost (denosumab-bbdz) is a RANK ligand (RANKL) inhibitor interchangeable biosimilar to Xgeva (denosumab) indicated for the prevention of skeletal-related events in patients with multiple myeloma or bone metastases from solid tumors, treatment of giant cell tumor of bone, and treatment of hypercalcemia of malignancy.	March 5, 2024
10.	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, Juvenile Idiopathic Arthritis	Tyenne (tocilizumab-aazg) Injection	Fresenius Kabi	Tyenne (tocilizumab-aazg) is an interleukin-6 (IL-6) receptor antagonist biosimilar to Actemra used for treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis.	March 5, 2024
11.	Esophageal Carcinoma	Tevimbra (tislelizumab-jsgr) Injection	BeiGene, Ltd.	Tevimbra (tislelizumab-jsgr) is a humanized immunoglobulin G4 (IgG4) anti-programmed cell death protein 1 (PD-1) monoclonal antibody indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.	March 13, 2024

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
12.	Nonalcoholic Steatohepatitis	Rezdiffra (resmetirom) Tablets	Madrigal Pharmaceuticals, Inc.	Rezdiffra (resmetirom) is a thyroid hormone receptor-beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).	March 14, 2024
13.	Metachromatic Leukodystrophy	Lenmeldy (atidarsagene autotemcel) Suspension for Intravenous Infusion - formerly OTL-200	Orchard Therapeutics	Lenmeldy (atidarsagene autotemcel) is an autologous hematopoietic stem cell (HSC) gene therapy for the treatment of children with metachromatic leukodystrophy (MLD).	March 18, 2024
14.	High Blood Pressure	Tryvio (aprocitentan) Tablets	Idorsia Ltd.	Tryvio (aprocitentan) is an endothelin receptor antagonist (ERA) for the combination treatment of hypertension that is not adequately controlled with other drugs.	March 19, 2024
15.	Pulmonary Arterial Hypertension	Opsynvi (macitentan and tadalafil) Tablets	Actelion Pharmaceuticals US, Inc.	Opsynvi (macitentan and tadalafil) is an endothelin receptor antagonist (ERA) and phosphodiesterase 5 (PDE5) inhibitor combination for the treatment of pulmonary arterial hypertension.	March 22, 2024

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
16.	Duchenne Muscular Dystrophy	Duvyzat (givinostat) Oral Suspension	Italfarmaco Group	Duvyzat (givinostat) is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy in patients 6 years of age and older.	March 21, 2024
17.	Pulmonary Arterial Hypertension	Winrevair (sotatercept) for Injection	Merck	Winrevair (sotatercept) is an activin signaling inhibitor used for the treatment of adults with pulmonary arterial hypertension.	March 26, 2024
18.	Anemia due to Chronic Kidney Disease	Vafseo (vadadustat) Tablets	Akebia Therapeutics, Inc.	Vafseo (vadadustat) is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least three months.	March 27, 2024
19.	Paroxysmal Nocturnal Hemoglobinuria	Voydeya (danicopan) Tablets	Astra Zeneca	Voydeya (danicopan) is a complement factor D inhibitor used for the treatment of extravascular hemolysis in adults with paroxysmal nocturnal hemoglobinuria.	March 29, 2024

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
20.	Schizophrenia	Risvan (risperidone) for Extended-Release Injectable Suspension	Laboratorios Farmacéuticos Rovi, S.A.	Risvan (risperidone) is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.	March 29, 2024

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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

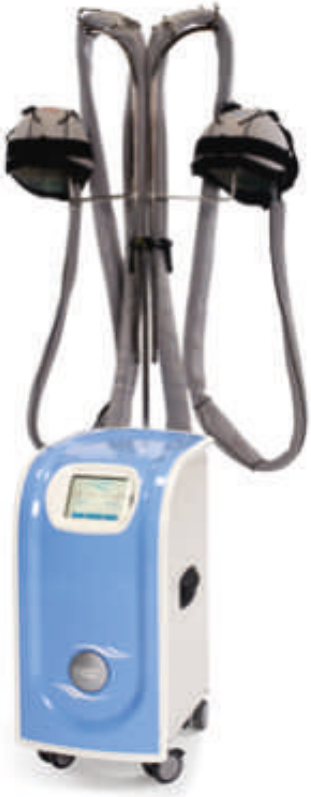
When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and to cooperate with the editor to retract or correct the paper in form of an erratum.

Disclaimer

PMCH
HEALTH ADVISORS

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

मातृत्व सुखम् भवः

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