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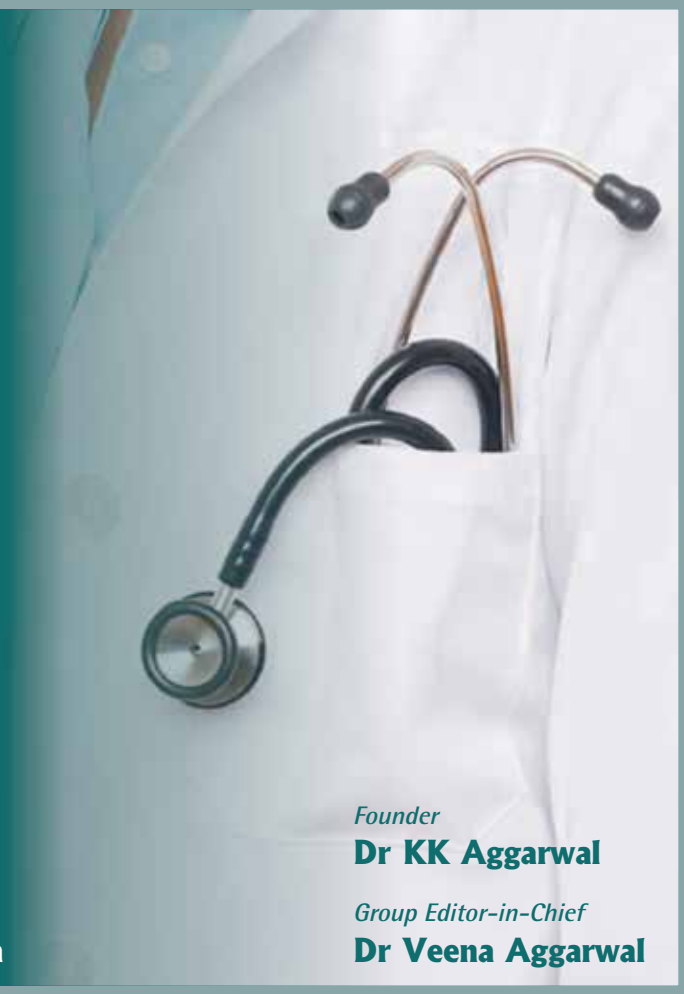



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# Frequent Use of Mobile Phones for Calls Linked to Risk of New-onset Hypertension?

Talking on mobile phones for a minimum of 30 hours in a week increases risk of new-onset hypertension by 12%. The risk increased 25% among those who used the phone for more than 6 hours in a week, according to a study published May 5, 2023 in the *European Heart Journal – Digital Health*.[1]

A total of 2,12,046 participants with a mean age of 54 years from the UK Biobank database were enrolled in this study to investigate if frequent use of mobile phones to make or receive calls was associated with incident hypertension. Of these, 62% were women. None of the participants had been diagnosed with hypertension at the time of their recruitment. Data on use of mobile phones was gathered through self-reported questionnaires, which revealed that 88% of the study subjects were mobile phone users, i.e., they used the mobile phone at least once per week to make or receive calls. The follow-up was for a period of 12 years during which 13,984 (7%) study participants developed incident hypertension.

People who were mobile phone users were at higher risk of developing new-onset hypertension with hazard ratio (HR) of 1.07. The risk increased in proportion to the weekly duration of phone use. The HR for weekly usage time of 30 to 59 minutes was 1.08; for 1 to 3 hours of use, the HR was 1.13; for 4 to 6 hours of use, the HR was 1.16 and for those with more than 6 hours of use, the HR was 1.25 compared to participants who used the mobile phone for calls for less than 5 minutes in a week.

The risk was increased 33% among those who were genetically predisposed to develop hypertension and also used their phones for longer hours (≥30 min) during the week with HR of 1.33 compared to use of phone for making or receiving calls less than 30 minutes and low genetic risk of hypertension.

This study has linked the use of mobile phones for making or receiving calls to increased risk of new-onset hypertension. The frequency of use influenced the risk of hypertension. This association was further augmented by genetic susceptibility to hypertension. However, the authors note that their study is an observational study and is "hypothesis-generating". These findings need to be confirmed in further studies. Nevertheless, the study cautions about the prudent use of mobile phones.

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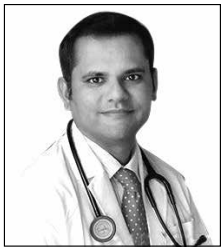

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# Meaningful Clinical Conversation: Guidance from the Gita

## ABSTRACT

Chronic disease care is a challenging vocation. One of the reasons for this is the need to inform and share decision making with patients. Communication and conversational skills are the pillars of chronic care delivery. In this editorial, we take guidance from the Srimad Bhagavad Gita in order to improve the quality of clinical conversations, and make them meaningful. The Gita encourages us to be 'saatvik' or balanced in thought, words and deeds, to perform 'penance' of mind, speech and body, and to accept equanimity. This introspective opinion piece should help us polish our communication skills, and improve interaction with our patients.

**Keywords:** Chronic care, diabetes, obesity, patient-centered care, person-centered care, psychosocial aspects

Chronic disease care is a challenging aspect of clinical medicine. To ensure that biomedical and psychosocial issues are addressed in a person-centered way, communication is very important. Health care professionals are cognizant of the fact that language matters.[1] Persons living with chronic disease, such as diabetes, obesity and cardiovascular disease, need sustained support and mindful motivation in order to ensure optimal self-care and management.[2] Using appropriate forms of communication is imperative in achieving this. Communication and conversation skills, therefore, must be integrated into medical and health care curricula.

## THE SRIMAD BHAGAVAD GITA

The Srimad Bhagavad Gita, the divine song of Lord Krishna, is a fountain of wisdom.[3] All health care providers need to work (i.e., perform penance and share sacrifices) in order to attain, and maintain the required professional competence.[4] In this communication, we discuss verses from the Gita which help us internalize pleasant, person-friendly language in chronic care practice.

The Gita is structured in eighteen chapters. Chapter 14 describes the three gunas or qualities of man: sattva, rajas and tamas. Chapter 16 differentiates between divine and demoniacal properties with Chapter 17 explaining this further in a three-pronged rubric. We use shlokas from these chapters to create reader-friendly suggestions for health care professionals.

## SATTVA AS A TOOL AND AS A TARGET

*"Sattva, Rajas and Tamas – these three gunas born of Nature tie down the imperishable soul to the body, Arjuna."* (14:5)

*"Of these Sattva, being immaculate, is illuminating and flawless, Arjuna; it binds through attachment to happiness and knowledge."* (14:6)

*"Arjuna, know the quality of Rajas, which is of the nature of passion, as born of desire and attachment. It binds the soul through attachment to actions and their fruits."* (14:7)

*"And know Tamas, the deluder of all those who look upon the body as their own self, as born of ignorance. It binds the soul through error, sloth and sleep, Arjuna."* (14:8)

*"When light and discernment dawn in this body, as well as in the mind and sense, then one should know that Sattva is predominant."* (14:11)

*"The reward of a righteous act, they say, is Sattvika, i.e., faultless in the shape of joy, wisdom and dispassion. __."* (14:16)

*"Wisdom follows from Sattva, __."* (14:17)

*"Those who abide in the quality of Sattva wend their way upwards__."* (14:18)

These verses describe three innate qualities of mankind: sattva, rajas and tamas. The reader may feel that being saatvik, i.e., being "immaculate, illuminating and flawless", is an ideal state, as it leads to "happiness and knowledge", promotes "wisdom" and allows one to "wend their way upwards". This means that the health care professional should aim for a saatvik disposition, of mind, body and senses. Having a saatvik temperament is a target in itself, and a tool towards mastering the art of meaningful conversation as well.

## THE MIND, BODY AND SPEECH

This can be accomplished by practicing austerity of the mind, penance of the body and penance of speech.

*"Worship of Gods, the Brahmanas, one's elders and great souls, purity, straight-forwardness, continence and non-violence – this is called penance of the body."* (17:14)

*"Words which cause no annoyance to others and are truthful, agreeable and beneficial, as well as the study of the Vedas and other Shastras and the practice chanting of Divine Name – this is known as penance of speech."* (17:15)

*"Cheerfulness of mind, placidity, habit of contemplation on God, control of the mind and perfect purity of inner feelings – all this is called austerity of mind."* (17:16)

*"This threefold penance performed with supreme faith by Yogis expecting no return is called Sattvik."* (17:17)

Table 1 lists these descriptions of penance in an alliterative, reader-friendly manner. Health care professionals should include these features in their daily routine, both personal and professional, with no expectations in mind. This will create a welcoming and friendly health care ecosystem which will foster saatvik communication as well as actions. This, in turn, will automatically lead to optimal health-related outcomes.

**Table 1.** Penance of the Mind, Speech and Body (Based on Srimad Bhagavad Gita 17:14-16)

| |
|---|
| **Penance of the body** |
| • Prayer |
| • Purity |
| • Plain speak |
| • Practice self-control |
| • Peaceful behavior |
| **Penance of speech** |
| • No Annoyance through words |
| • Accurate |
| • Agreeable |
| • Advantageous |
| • Almighty remembrance |
| **Penance of mind** |
| • Cheerfulness |
| • Calmness |
| • Contemplation on God |
| • Control of mind |
| • Clean thoughts |

## EQUANIMITY AND EQUIPOISE: A DIVINE GIFT

The above discussion is incomplete, however. Saatvikta cannot exist in isolation, and our environment, both physical and psychosocial, may not always be conducive to, or accepting of, saatvik behavior. As health care professionals, we may be exposed to unpleasant attitudes, behaviors and actions, and ourselves exhibit traits of raajsik or taamsik behavior. Are these acceptable?

The Bhagavad Gita has an answer to this as well.

*"He who sees that all actions are performed in every way by nature (Prakriti) and the Self as the non-doer, he alone verity sees."* (13:29)

*"___ he who hates not light (which is born of Sattva) and activity (which is born of Rajas) and even stupor (which is born of Tamas), when prevalent, nor longs for them when they have ceased."* (14:22)

*"He who is equipoised in honor or ignominy, is alike towards a friend or an enemy, and has renounced the sense of doership in all undertaking, is said to have risen above the three gunas."* (14:25)

**Table 2.** Features of a Person Born with Divine Gifts (Based on Srimad Bhagavad Gita 16:1-3)

- Holistic hygiene: Composure, control and cleanliness of mind, body and sense
- Harm no one: Non-violence in thought, word and deed, with abstinence from malice and anger
- Humility: Absence of self-esteem, sense of doership and attachment to senses
- Helpful nature: Compassion, charity, worship and Vedic study
- High sense: Sense of duty willingness to suffer hardships for the sake of duty, and sense of shame in transgressing scriptures

We should view all persons, all behaviors and all situations with equanimity. Chapter 16, verses 1 to 3, describe the characteristics of a person who is born with divine gifts. These include perfect purity of mind, control of the senses, non-violence in thought, word and deed, absence of anger even on provocation and compassion towards all creatures.

We should strive to "control the senses" (16:1) and "avoid anger even on provocation" (16:2). Table 2 paraphrases the 21 features of a "divine" person, as mentioned in these verses, into 5 overarching descriptions. Holistic hygiene, harming none and helping all, with humility and a high sense of purpose, are the attributes of an evolved person, and his/her conversation.

The health care profession is a divine calling, one that can make a difference between life and death. Keeping this in mind, we should aim to inculcate these "divine gifts" in our thoughts, words and actions. This can be done through penance of mind, speech and body, as described in Chapter 17 (Table 1). While we target Saatvikta in every sphere of life, we should be open to encountering, and accepting, raajsik and taamsik situations as well. These should be handled dispassionately.

## SUMMARY

As we endeavor to help our patients with chronic disease live healthy and happy lives, we will certainly face challenges. Many of these can be tackled by effective counseling. The Srimad Bhagavad Gita guides us in polishing our conversational skills, which can help us communicate better with our patients, and their caregivers. This will assist in making clinical conversations meaningful and thereby, contribute to optimization of health for all.

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### NITI Aayog Report: Kerala Emerges Top-performing State in Health Sector in the COVID Year 2020-21

Kerala has been identified as the state with the best performance in the health sector for the COVID year 2020-21 as per the most recent report by NITI Aayog. The state achieved the top spot among the 19 "larger states" in the annual health index for 2020-21. Telangana and Tamil Nadu took second and third place, respectively. On the other hand, the bottom three states on the list are Madhya Pradesh (17), Uttar Pradesh (18) and Bihar (19). Notably, Kerala also held the top spot in the report from the previous year. Tripura took first place among the smaller states, followed by Sikkim and Goa in second and third, respectively. The bottom three states on the list are Manipur (eighth), Nagaland (seventh) and Arunachal Pradesh (sixth). Compared to prior years, Rajasthan, Uttarakhand and Odisha showed increased performance. The Union Territories list was headed by Lakshadweep, with Delhi at the bottom.

The newborn mortality rate, the gender ratio at birth, and vaccination coverage are only a few of the 24 indicators used to compute the health index. Since 2017, NITI Aayog has used this methodology to evaluate the health index, considering overall performance and improvement over time. The World Bank and the Union Ministry of Health and Family Welfare worked together to create the index. (*Source: https://english.mathrubhumi.com/news/kerala/kerala-retains-top-position-in-health-index-of-niti-ayog-for-2020-21-1.8592039*)

REVIEW ARTICLE

# Clinical Efficacy of Piracetam in the Management of Acute Stroke and Post-Stroke Sequelae: An Expert Panel Review and Opinion

VIKRAM SHARMA*, SANJAY KUMAR CHOUDHARY†, SUNIL KUMAR YADAV Y‡, SNEHAL MUCHHALA‡, AMEY MANE‡, BHAVESH KOTAK‡

## ABSTRACT

Stroke is a major cause of death worldwide. Prompt treatment and decision-making is essential for good outcomes. The two major therapeutic approaches for acute ischemic stroke are thrombolytics and neuroprotectants. Piracetam, a nootropic drug aims to increase cerebral blood flow, enhance oxygen extraction, restore membrane fluidity and modulate neurotransmission. Likewise, citicoline has been shown to positively influence cerebral plasticity and neurorepair processes. The present article aims to offer insights on the current management of acute stroke and to position piracetam and its combination with citicoline in the management of acute stroke and post-stroke sequelae based on an expert panel discussion.

**Keywords:** Citicoline, neuroprotectants, piracetam, thrombolytics, stroke

Stroke, described as a clinical syndrome comprising of rapidly emerging clinical signs of focal disturbance of cerebral function for more than 24 hours or resulting in death with no apparent cause other than a vascular origin, is the second leading cause of death globally.[1,2] It is estimated to be the third most common cause of disability worldwide.[1] The prevalence of incident strokes, stroke-survivors, stroke-related deaths and disability-adjusted life-years is escalating extensively.[2] Stroke can be broadly classified as ischemic stroke, accounting for 68% of all strokes and hemorrhagic stroke constituting 32%.[1] This article aims at describing the management of stroke and the positioning of piracetam and its combination with citicoline in the management of acute stroke and post-stroke sequelae.

## METHODS

In 2021, two expert group meetings were conducted virtually involving 29 neurologists from various cities in India namely, Hyderabad, Delhi, Kolkata, Mumbai, Patna, Bangalore, Varanasi, Chennai, Madurai, Coimbatore, Lucknow, Amravati, Vizag, Pune, Siliguri, Jamnagar, Pilibhit, Sangli, Durg, Rohtak and Bhopal. The main purpose of these meetings was to discuss and understand various aspects of managing acute stroke with an emphasis on the clinical role of piracetam and its combination with citicoline.

## MANAGEMENT OF ACUTE STROKE

Every minute, atypical patient with ischemic stroke loses 190,0000 brain cells, while approximately 14000,000,000 nerve connections are damaged and 7.5 miles of nerve fibers are lost.[1] Hence, a condition like stroke requires prompt treatment and decision-making, and round-the-clock preparedness for hospitals to ensure evidence-based care, which is crucial for good outcomes in stroke. Revascularization and limitation of secondary neuronal injury are the prime goals of advanced stroke management.[3] Two major types of therapeutic approaches to acute stroke are: 1) Thrombolytics to restore cerebral blood flow; 2) Neuroprotectants to target cellular pathways to preserve brain function, enhance neuronal repair and promote recovery. The present effective treatment modalities for acute ischemic stroke are intravenous thrombolytic therapy within 4.5 hours of onset and intra-arterial thrombectomy within 6 hours of stroke onset.[4]

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Adjunctive treatments delivered in combination with intravenous thrombolysis for ischemic stroke, either pharmacological or nonpharmacological, provide an array of therapeutic effects, including anti-inflammatory, antiexcitotoxicity, antioxidizing cerebral metabolism reducing and apoptosis-adjusting effects.[5,6] Thrombolysis therapy enhances the therapeutic effect of neuroprotective agents, as oxygen and nutrient supply restored after thrombolysis are the prime factors for neuronal survival. The neuroprotective action will be augmented once the occluded artery is reopened, as neuroprotective agents partially work by lowering the ischemia-reperfusion injury. Moreover, neuroprotectants utilized as adjunctive therapy also have the potential to attenuate ischemic injury in the penumbra area, lengthen the thrombolytic time window and lower the risk of symptomatic intracranial hemorrhage by stabilizing the blood-brain barrier.[6] Currently used nootropics include pyrrolidinone derivatives like piracetam, oxiracetam, aniracetam and promiracetam as well as natural products like *Ginkgo biloba, Bacopa monnieri, Rhodiola rosea,* etc.[7] The other adjuvant pharmacological therapies include those that preserve blood-brain barrier (e.g., atorvastatin, batimastat, candesartan, cilostazol, fasudil, minocycline, etc.), improve vascularization, protect the cerebrovasculature (e.g., coumarin derivate IMM-H004 and granulocyte-colony stimulating factor) and deploy their effects through other mechanisms of action (e.g., oxygen transporters, ascorbic acid, etc.).[5] The nonpharmacological therapies include stem cell treatments, gas therapy, hypothermia and remote ischemic conditioning with multidimensional biological effects.[5,6] Figure 1 illustrates the algorithm for multimodal management of stroke.[8,9]

**Consensus Opinion 1**

*The National Institutes of Health Stroke Scale (NIHSS) is used universally for all patients to assess the severity, apart from computed tomography (CT), angiography and magnetic resonance imaging (MRI).*

*The levels of inflammatory markers, C-reactive protein (CRP) and D-dimer levels should be measured and anticoagulant and antiplatelet medications must be prescribed to patients.*

## POSITIONING OF PIRACETAM IN MANAGEMENT OF ACUTE STROKE, POST-STROKE APHASIA AND OTHER CONDITIONS

Piracetam, the first nootropic drug, is a cyclic derivative of the neurotransmitter gamma-aminobutyric acid (GABA). Although the mode of action has not yet been fully elucidated, studies have reported that it influences neuronal and vascular functions. Its neuronal effects include an impact on neurotransmission by influencing cholinergic, serotoninergic, noradrenergic and glutamatergic systems. Piracetam has been found to increase the number of post-synaptic receptors and restore their function.[10] Additionally, it offers neuroprotective effects by restoration of neurotransmission and improvement of metabolism. The anticonvulsant effects of piracetam have been shown to reduce seizure severity and enhance anticonvulsant action of other drugs such as carbamazepine and diazepam. Its vascular effect is translated by an antithrombotic effect leading to improvement of microcirculation and decreasing platelet aggregation.[10,11]

In congruence with its numerous pharmacological effects, piracetam has documented efficacy in a diverse range of indications. Piracetam is indicated in the management of vertigo, dyslexia, cortical myoclonus and sickle cell anemia in addition to age-related cognitive disorders. It is a well-tolerated drug and its benefits in these conditions appear to result from an array of neuronal and vascular effects associated with restored membrane fluidity.[10]

The basis for the use of piracetam in acute stroke is the combination of its neuroprotective, hemorheological and antithrombotic properties. Piracetam has been shown to increase compromised regional cerebral blood flow in patients with acute stroke and to improve clinical outcomes when administered soon after symptom onset.[12]

A hospital-based observational study by Chen et al evaluated the association of piracetam use and the clinical characteristics of NIHSS changes in patients enrolled based on 2,483 stroke registration data cohorts. Multivariate analysis showed significant improvement in NIHSS scores with piracetam use. Subgroup analysis revealed the efficacy of piracetam in the following patient groups: age ≥75-year-old, male gender, normal weight, obesity, ex-smokers, patients with hypertension, dyslipidemia, without diabetes mellitus and without atrial fibrillation. Thus, selection of clinical characteristics under which piracetam treatment should be given is important for NIHSS improvement of ischemic stroke patients.[4]

Aphasia is a common symptom following a stroke.[13] Studies on piracetam in post-stroke aphasia patients have shown elevation of cerebral blood flow and glucose metabolism in infarcted and penumbral tissues and to be an effective adjunct of verbal skills.[4] Piracetam

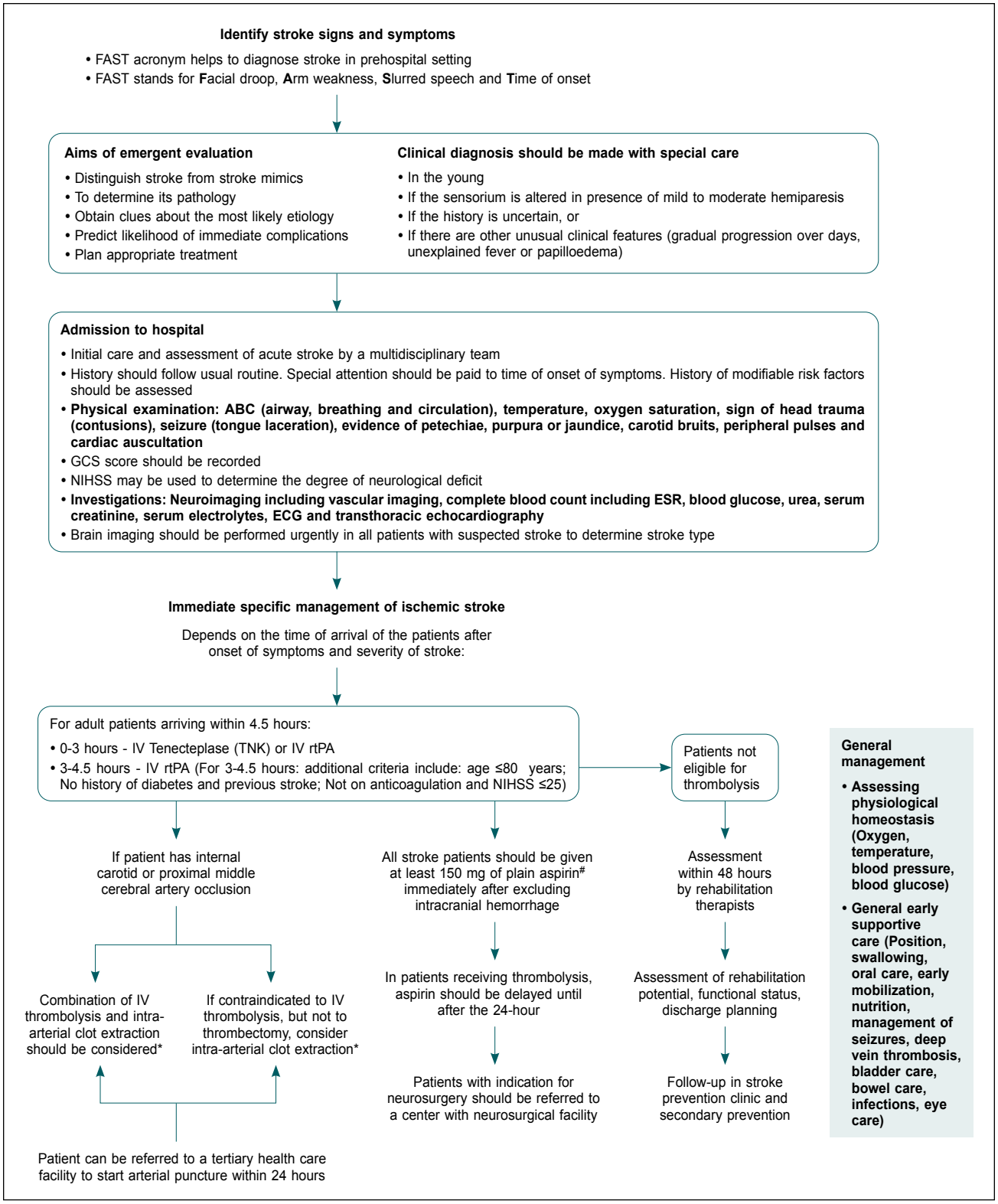


**Figure 1.** Multimodal management of stroke algorithm (Developed from: Guidelines for prevention and management of stroke 2019; Van Bussel EF, et al.).

*If they have internal carotid or proximal middle cerebral artery occlusion causing a disabling neurological deficit.

#Patients with acute ischemic stroke who are allergic to or intolerant of aspirin should be given an alternative antiplatelet agent (e.g., clopidogrel).

GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale; ESR = Erythrocyte sedimentation rate; rtPA = Recombinant tissue plasminogen activator.

in combination with speech and language therapy has the potential to facilitate rehabilitation from acute and chronic aphasia, indicating clinical support for its use in post-stroke aphasic patients.[13]

### Consensus Opinion 2

*Piracetam has a role in the management of acute stroke in effectively improving NIHSS and Barthel index in stroke patients. It also has a definitive role in long-term treatment of patients with post-stroke aphasia. Table 1 provides an overview on the dosage regimen of piracetam in acute stroke and post-stroke.*

## POSITIONING OF PIRACETAM AND CITICOLINE COMBINATION IN THE MANAGEMENT OF ACUTE STROKE, POST-STROKE APHASIA AND OTHER CONDITIONS

With several overlapping processes leading to either damage or protection, the pathology of stroke is complex. Even if substantial neuroprotection can be achieved by aiming at just one of these processes, the probable benefit is even more if various mechanisms of damage can be repressed at the same time. Accordingly, combination therapy with more than one drug has proven to be effective in multiple experimental studies.[14]

Citicoline, a drug that provides neurovascular protection and repair effects with an excellent safety profile, is indicated in patients with acute ischemic stroke and other neurological disorders. A meta-analysis of trials of citicoline in acute and subacute stroke suggested a beneficial and substantial treatment effect, with absolute reductions of up to 12% in the rates of disability and long-term deaths. The odds ratio was 33% higher compared to the placebo with respect to the complete functional and neurological recovery in patients with moderate to severe acute ischemic stroke treated with oral citicoline for 6 weeks.[15] The effect of citicoline is correlated with the mechanisms that regulate cerebral plasticity and neurorepair processes. Based on its therapeutic effect, citicoline is used in the management of several nervous system dysfunctions which include dementia, memory loss, depressive disorders and Parkinson's disease.[16]

Combination of citicoline and piracetam can be a beneficial option in the management of various cognitive disorders. As the combination can cross the blood-brain barrier, it can easily enter the cerebrospinal fluid of the brain. The combination can be used in memory enhancement, neurological and cognitive disorder, Parkinson's disorder, Alzheimer's disorder, depression and anxiety, closed craniocerebral trauma, dyspraxia clotting, coagulation and vasospastic disorders.[17]

### Consensus Opinion 3

*Piracetam and citicoline can be used as sequential therapy or combination therapy for stroke or post-stroke aphasia.*

*Oral piracetam can be started at 1.2/2.4/4.8 g per day and titrated as per response followed by 1 g per day citicoline or vice versa for 3 to 4 weeks and maintenance of either of the drug for a longer duration (or at least 9-12 months) or combination therapy as mentioned in Table 2. Both the drugs are safe for long-term use.*

*In the Indian scenario, there exist some discrepancies of opinions regarding the use of piracetam and citicoline in the management of acute stroke as their definitive role in patients with acute stroke requires additional exploration. There is a need of strong clinical data support of piracetam and its combination with citicoline to establish its efficacy in acute stroke.*

## STROKE AND IMPACT OF COVID-19

Coronavirus disease 2019 (COVID-19) infection has been linked with an increased risk of ischemic stroke. A 10-fold elevated incidence of ischemic stroke during the 14 days after COVID-19 diagnosis as compared with the control interval was reported. Even when the risk interval was extended to 21 and 31 days after COVID-19 diagnosis, the incidence of ischemic stroke remained significantly high.[18] Moreover, severe COVID-19 disease

**Table 1.** Dosage Regimen of Piracetam in Acute Stroke and Post-Stroke

| Indications | Dosage regimen based on expert opinion |
|---|---|
| Acute stroke | Within 12 hours of presentation, piracetam 12 g IV bolus administered over 20 minutes followed by 3 g 6 hourly IV for 3 to 5 days as per response and followed by oral maintenance therapy for 1 to 3 months. |
| Post-stroke | Piracetam 1.2 to 2.4 g per day orally for a longer duration or at least 9 to 12 months. |

IV = Intravenous

**Table 2.** Dosage Regimen of Piracetam and Citicoline Combination in Acute Stroke and Post-Stroke

| Indications | Dosage regimen based on expert opinion |
|---|---|
| Acute stroke | Piracetam can be started with 1.2/2.4/4.8 g as per response followed by 1 g citicoline for 3 to 4 weeks. |
| Post-stroke | Combination of piracetam 800 mg and citicoline 500 mg twice a day orally for 1 to 3 months. |

occurred more frequently in elderly patients who are more likely to have multiple comorbidities; these patients also are more susceptible to incidence of strokes.[19] Cytokine storm development, innate immune system stimulation, propagation of embolic events by existing or new-onset arrhythmias, hypoxia-induced ischemia ancillary to severe pulmonary disease, thrombotic microangiopathy, endotheliopathy/endothelialitis and multifactorial activation of coagulation are the key proposed mechanisms of COVID-19 associated stroke. Literature supports raised levels of D-dimer in COVID-19 infected patients experiencing an acute ischemic stroke, signifying activation of the coagulation and innate immune system. A cytokine storm leading to increased levels of both interleukin-6 and CRP is considered to be associated with the risk of stroke in COVID-19 patients.[19]

The "Indian Stroke Association" had issued a consensus statement to provide a treatment model for patients who have suffered a stroke in the pandemic. In a positive or suspected COVID-19 patient, rapid screening should be done in the screening areas for patients presenting with stroke; evaluation and management should be undertaken without delay. Taking into account the time sensitive nature of the disease, the primary contact hospital can consider managing the patient in the acute phase of stroke; in case shifting of the patient is not possible to the designated COVID-19 hospital on time. The patient could then be referred to the designated COVID-19 hospital as soon as possible with prenotification and a suitable transfer method.[20]

### Consensus Opinion 4

*The prevalence of stroke has increased since the COVID-19 outbreak. The incidence of acute ischemic stroke was about 1% to 2% in practice since the outbreak. This increase in prevalence was due to the deranged lifestyle changes, decrease in regular follow-up visits due to ongoing restrictions, COVID peaks and due to COVID-19 infection directly. In COVID-19 positive patients with 2 or more weeks of pulmonary symptoms, and individuals who have recovered from COVID-19, there is increased presentation of stroke, which can be attributed to the increased pro-inflammatory cytokines and increased risk of thromboembolism with or without haemorrhagic component.*

## CONCLUSION

Prompt treatment of stroke can prevent long-term disability and death. Management of stroke comprises of a multidisciplinary approach that starts and extends beyond hospital admission. Piracetam, a nootropic drug, with its several neuronal and vascular effects, has proven beneficial in several conditions including age-related cognitive disorders, vertigo, cortical myoclonus, dyslexia and sickle cell anemia. Combination of piracetam with citicoline–a drug that combines neurovascular protection and repair effects, can be potent in the management for various cognitive disorders. Literature supporting the benefits of piracetam and citicoline in the treatment of cognitive disorders are numerous, although potential beneficial effects of piracetam and its combination with citicoline remain unclear in stroke patients because of insufficient well-controlled studies.

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### Conflict of Interest

Dr Sunil Kumar Yadav Y, Dr Snehal Muchhala, Dr Amey Mane and Dr Bhavesh Kotak are employees at Dr. Reddy's Laboratories. The other authors have no conflicts of interest.

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### Study: Alzheimer's Genes Might Increase Risk of Epilepsy

Research published in *Neurology* stated that persons who have a genetic tendency for Alzheimer's disease might have an increased risk of epilepsy, and those who have a specific form of epilepsy may have an increased chance of getting Alzheimer's disease.

Researchers examined gene variation throughout the human genomes of 1,11,326 people with Alzheimer's disease and 6,77,663 people without the condition using a genome-wide association analysis. They utilized a study strategy known as Mendelian randomization to see if there was a link between genetic variants and epilepsy risk.

Alzheimer's disease was shown to be associated with a 5.3% greater risk of generalized epilepsy and a 1.3% increased risk of localized epilepsy with hippocampal sclerosis. They also discovered that genes that indicated a lesser level of an Alzheimer's disease biomarker were associated with an increased likelihood of generalized epilepsy.

Experts say those with focal epilepsy and hippocampal sclerosis is roughly four times more likely to acquire Alzheimer's disease than people without epilepsy. (*Source:https://theprint.in/science/having-alzheimers-genes-may-increase-risk-of-epilepsy-study/1593410/*)

CLINICAL STUDY

# Vascular Calcification in Chronic Kidney Disease Patients on Hemodialysis: Prevalence and Correlation with Vascular Disease Events

FAYAZ AHMAD WAR*, MANJU AGGARWAL†, SOURABH SHARMA‡

## ABSTRACT

**Introduction:** With declining kidney function, the prevalence of vascular calcifications increases and calcification occurs years earlier and is more severe in chronic kidney disease (CKD) patients than in general population. We did this study to find the prevalence of vascular calcification in patients on maintenance hemodialysis using simple and inexpensive radiological method and to find out the correlation of vascular calcification score with vascular disease events, cardiovascular and all-cause mortality over a follow-up period of 1 year. **Materials and methods:** This prospective, observational, comparative, follow-up, single-center study of maintenance hemodialysis patients was performed at a tertiary care center in Haryana. Seventy-one patients on maintenance hemodialysis for more than 3 months were included in the study. Patients who were 18 years of age or below, CKD stage 5 patients not on dialysis and those who had previous history of parathyroidectomy were excluded. Adragao score for vascular calcification was calculated by evaluating bilateral iliac, femoral and radial arteries in plain radiographic films of pelvis and hands. Statistical analyses were performed with the SPSS System 10.0. **Results:** Seventy-one patients were enrolled in this study out of which, 45 were male and 26 were female. Mean age of patients was 61.92 ± 10.77 years. Majority of patients were elderly (age group ≥60 years). Out of 71 patients, 66 (92.9%) were hypertensive and 26 (36.6%) patients were diabetic. Twenty-two (30.9%) patients had cardiovascular disease (CVD) at baseline. Coronary artery disease (CAD) was present in 20 (28.1%) patients, cerebrovascular disease was present in 2 (2.8%) patients and peripheral artery disease (PAD) was present in only 1 patient at baseline. Average dialysis duration received by patients was 21.35 ± 21.17 months. Out of 71 patients, 16 (22.5%) received calcium-containing phosphate binder, 51 (71.8%) received noncalcium-containing phosphate binder and 4 patients received no phosphate binder. Fifty-five (77.4%) patients received therapeutic or prophylactic vitamin D3 therapy during the study period. Vascular calcification detected with plain X-ray of pelvis and both wrists was found in 56.3% of patients on maintenance hemodialysis. The prevalence and severity of vascular calcification was higher with increasing age. Diabetes was found to be significantly associated with the presence of vascular calcification ($p < 0.0005$). CAD at the time of enrollment was significantly associated with vascular calcification ($p = 0.009$). Serum levels of calcium, phosphate, vitamin D3, intact parathyroid hormone (PTH), calcium-phosphate product or use of phosphate binders or the types or vitamin D therapy did not correlate clinically with presence of vascular calcification. Hemodialysis duration did not correlate with the presence of vascular calcification ($p = 0.113$). Presence of vascular calcifications in hemodialysis patients predicted future vascular disease events over 1 year follow-up ($p = 0.013$) but did not correlate with cardiovascular and all-cause mortality. **Conclusion:** There is a high prevalence of vascular calcification in maintenance hemodialysis patients in our center. The risk factors of vascular calcification were higher age, diabetes and CAD. These patients should be followed-up regularly for vascular events. We also want to reiterate with this study that plain X-ray is sufficient to rule out vascular calcification in CKD patients and should be employed regularly in dialysis clinics.

**Keywords:** Vascular calcification, chronic kidney disease, hemodialysis, vascular diseases

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Vascular calcification is a process characterized by thickening and loss of elasticity of muscular artery walls. There are two main types of vascular calcifications in chronic kidney disease (CKD) patients on hemodialysis: (i) common atherosclerosis, with intimal patchy calcifications of atherosclerotic plaques and (ii) medial sclerosis with medial linear calcifications that seem to be related to mineral metabolism disturbances.[1] Arterial medial calcification is an active process in

response to pathological conditions, including aging,[2] inflammation, diabetes, CKD and phenotypic switch of resident cells.[3] With declining kidney function, the prevalence of vascular calcifications increases and calcification occurs years earlier and is more severe in CKD patients than in the general population. The phenotype of vessels of younger dialysis patients is comparable with that of octogenarians without CKD.[4] The prevalence of vascular calcifications among patients with CKD, especially those on hemodialysis, is extremely high (>80%);[5] its prevalence increases with progressive fall in glomerular filtration rate (25% in stage 3 and 35% in stage 4)[6] and is present in over 50% of patients at the time of initiation of renal replacement therapy (RRT).[7] Some concern has been raised that the high prevalence and severity of vascular calcification among CKD patients may be related to the administration of calcium-containing phosphate binders used to treat hyperphosphatemia. However, vascular calcification was a frequent feature of patients with CKD prior to the availability of calcium-containing phosphate binders.[8]

This suggests that calcium-containing phosphate binders alone do not explain the high prevalence of vascular calcifications among CKD patients. It is possible that the increasingly high prevalence may be the result of a greater number of elderly and diabetic patients, and better technologies for assessment and quantification of vascular calcification. Several risk factors may induce arterial calcification leading to accelerated vascular aging. They are divided into "classic" risk factors such as age, gender, CKD and dialysis vintage, inflammatory status, disorders of calcium and phosphate, diabetes and "non-classic" factors such as abnormal levels of bone-related proteins: fetuin-A, matrix-carboxyglutamic acid protein (Matrix-Gla protein, MGP), pyrophosphate, osteoprotegerin and bone morphogenetic protein-2.[9]

These factors also influence each other, for example, the reduction of renal function promotes the development of inflammation (increase of C-reactive protein and reduction of fetuin-A) that contribute to endothelial dysfunction and vascular calcification. Increasing age and time on dialysis are major risk factors for vascular calcification. This was demonstrated in a comprehensive systematic review of 30 studies over a period of 20 years that showed that age and length of time on dialysis therapy were the main factors associated with vascular calcification among patients with CKD.[10] Among patients without CKD; many studies have shown that diabetes is a risk factor for vascular calcification. Among CKD patients, diabetes also increases the risk of vascular calcification. Poorly controlled hyperphosphatemia often increases the requirement for calcium-containing phosphate binders, which then increases the risk of recurrent concomitant hypercalcemia. Most experts believe that a raised plasma phosphate with intermittent or persistent hypercalcemia drives the initiation and progression of vascular calcification.[11] There appears to be relatively less progression of vascular calcification with sevelamer versus calcium-containing phosphate binders among dialysis patients. Clinically employed doses of vitamin D frequently result in hypercalcemia and an elevated calcium-phosphate (Ca x P) product, which can accelerate extraosseous calcification.[12]

Important mechanisms of vascular calcification in CKD patients are the failure of inhibitory systems for vascular calcification and differentiation of vascular smooth muscle cells (VSMCs) to osteoblast-like cells. Inhibitory factors for vascular calcification include MGP, pyrophosphate (produced in VSMCs) and circulating inhibitor fetuin-A. On the other hand, activation of transcription factors "Runx2" and mineralization regulating protein "alkaline phosphatase (ALP)" are important key factors for osteochondrocytic differentiation of VSMCs. Uremic milieu concomitantly inactivates the production of inhibitors and promotes phenotypic changes and/or apoptosis of VSMCs resulting in medial calcification.[13] Several reports have shown the strong relationship between vascular calcification and clinical outcomes including cardiovascular events, and cardiovascular and all-cause mortality. The number of calcified sites was a strong predictor of cardiovascular and all-cause mortality.[14] Dialysis patients with higher vascular calcification scores have significantly higher rate of cardiovascular events, cardiovascular and all-cause mortality compared with those with mild or no calcification score.[15] A number of noninvasive methods have been developed for the detection and quantification of vascular calcification. Electron-beam computed tomography (EBCT) scan detects and quantifies vascular calcification, and is a more sensitive method for detection of vascular calcifications. However, it is a very expensive method and does not differentiate between intimal and medial calcium deposition. The simplest technique is plain radiography, which demonstrates pipe-stem calcification of the tunica media and more irregular, patchy calcifications of the internal elastic lamina. Plain films may differentiate between intimal and medial calcification to some degree.[16]

Plain films are, however, less sensitive compared to EBCT. The use of plain radiographic films for vascular calcification assessment has been suggested in the recent KDOQI clinical practice guidelines.[17] The main aim of this

study was to find the prevalence of vascular calcification in patients who are on maintenance hemodialysis in our center using a simple and inexpensive radiological method for diagnosis of vascular calcifications, and to find out the correlation of vascular calcification score with vascular disease events (coronary artery disease [CAD], cerebrovascular disease and peripheral artery disease [PAD]), cardiovascular and all-cause mortality over a follow-up period of 1 year. The timely diagnosis of vascular calcifications and the identification of possible contributing factors raise the hope for a possible primary, and therapeutic intervention that might reduce cardiovascular and other vascular diseases risk in hemodialysis patients.

## MATERIALS AND METHODS

### Place of Study

Department of Nephrology, Artemis Hospitals, Gurugram, Haryana, India.

### Study Design

This was a prospective, observational, comparative, follow-up, single-center study of maintenance hemodialysis patients.

### Patient Population

Seventy-one patients who were on maintenance hemodialysis for more than 3 months were included in the study. Patients who were 18 years of age or below, end-stage renal disease (ESRD) patient not on dialysis and those who had previous history of parathyroidectomy were excluded from the study. Among the enrolled patients, those who had no vascular calcifications, were taken as controls.

### Collection of Data

A proforma providing all historical, clinical and treatment details during the course of study was used to record patient data. The following data of all patients was collected at the time of enrollment in the study: demographic profile, basic renal disease, hemodialysis duration, comorbidities like diabetes, hypertension, CAD at baseline, phosphate binder used, vitamin D therapy and calcium intake. Serum calcium, serum phosphorus, ALP, serum albumin, serum 25-hydroxyvitamin D [25(OH)D] levels and intact parathyroid hormone (PTH) were measured in all the patients. Dialysate calcium concentration of 1.75 mmol/L was used in our Dialysis center for all patients. All patients were subjected to plain X-rays (anteroposterior view) of pelvis and both wrists at the time of inclusion in the study. The X-rays were reported by an experienced radiologist who was blinded to the clinical profile of patients. A simple vascular calcification score developed by Adragao et al[18] was used to evaluate vascular calcifications.

### Adragao Score

This vascular calcification score was evaluated from bilateral iliac, femoral and radial arteries in plain radiographic films of pelvis and hands. The pelvis radiographic films were divided into four sections by two imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. The films of the hands were divided, for each hand, by a horizontal line over the upper limit of the metacarpal bones. The presence of linear calcifications in each section was counted as 1 and its absence as 0. The final score was the sum of all the sections, ranging from 0 to 8.[18] Vascular calcifications were deliberately evaluated only in muscular arteries: iliac, femoral, radial and digital. Pelvic films evaluated iliac and femoral arteries (Fig. 1); wrist films evaluated radial and digital arteries (Fig. 2). Only linear calcifications, with or without patchy calcifications, were considered for the final calcification score, because they outline the vessel wall and have undoubtedly vascular localization. Patchy isolated calcifications that may be associated with intimal calcifications were not considered in this score.

Serum calcium was measured by indirect ion selective electrode method and serum phosphate by phosphomolybdate method, on UniCel DxC 800 Synchron Clinical System. ALP was measured by P-nitrophenyl phosphate AMP-Buffer method and albumin by bromocresol purple method, both were measured on UniCel DxC 800 Synchron Clinical System. Vitamin D (25-hydroxy) was measured by enzyme-linked fluorescent assay on MiniVIDAS which is a multiparametric immunoanalyzer. Intact PTH levels were measured using chemiluminescence immunoassay on UniCel DxC 860i Synchron Access Clinical System. Patients were followed over a period of 12 months from March 2016 to February 2017.

All vascular disease events (CAD, CVD and PAD), were recorded in detail over 1 year. CAD was diagnosed if the patient developed typical angina pectoris, had positive stress test, had acute coronary syndrome (ACS), or underwent percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG), or if the patients had regional wall motion abnormality (RWMA) on 2D Echo. The diagnosis of

cerebrovascular disease was based on occurrence of stroke or transient ischemic attack (TIA) or detection of old infarct on CT/MRI (magnetic resonance imaging) brain. PAD was diagnosed if there was history of claudication, ischemic ulcers, lower limb amputations or diagnosis by Doppler or angiography.

## ETHICAL CONSIDERATION

Before the commencement of study, informed and written consent was obtained from all the patients selected for the study after explaining the risks and benefits associated with the study. The aim and the value of work was explained to them. Participation of patients was voluntary and their data was kept confidential.

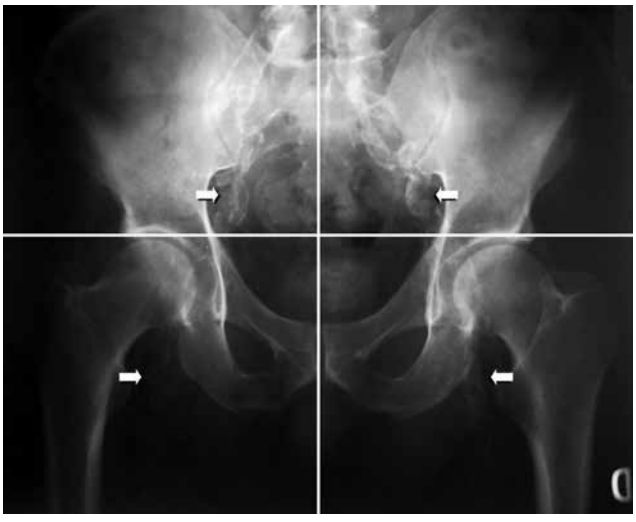

**Figure 1.** Vascular calcification score - Pelvic films to evaluate iliac and femoral arteries.

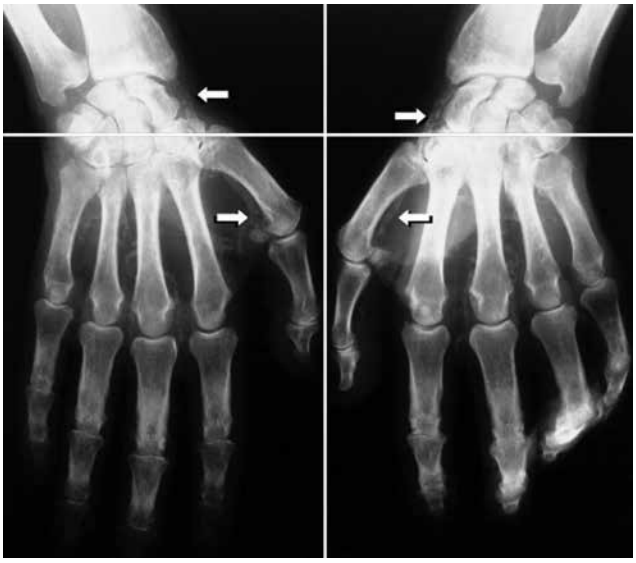

**Figure 2.** Vascular calcification score - Wrist films to evaluate radial and digital arteries.

## STATISTICAL ASPECTS

Variables were expressed as frequencies, percentages for discrete factors and mean values for normally distributed continuous factors. Statistical comparisons of baseline characteristics and end points were performed using the two-tailed Chi-square test. The independent variables associated with vascular calcifications, vascular disease at baseline and vascular disease at the end of follow-up were identified by binary logistic regression models. Covariates for vascular calcification analysis were age, sex, diabetes, hemodialysis duration, calcium, phosphate, Ca x P product, vitamin D3 and intact PTH. Statistical analyses were performed with the SPSS System 10.0. For all comparisons, a p-value of $<0.05$ was considered statistically significant.

## RESULTS

Seventy-one patients were enrolled in this study out of which, 45 were male and 26 were female. The demographic characteristics of the patients has been depicted in Table 1. Mean age of patients was 61.92 ± 10.77 years. Majority of patients were elderly

**Table 1.** Demographic, Clinical and Laboratory Characteristics of Patients Studied

| Patient characteristic | Mean ± SD or No. (%) of patients |
|---|---|
| Age | 61.92 ± 10.77 |
| Male | 45 (63.38) |
| Female | 26 (36.61) |
| Basic disease | |
| Diabetic nephropathy | 26 (36.61) |
| Nondiabetic | 45 (63.3) |
| Comorbidities | |
| Hypertension | 66 (92.95) |
| Diabetes | 26 (36.61) |
| CVD | 22 (30.98) |
| Others | 40 (56.33) |
| Serum calcium | 8.33 ± 0.79 |
| Serum albumin | 3.36 ± 0.47 |
| Corrected calcium | 8.81 ± 0.85 |
| Serum phosphorus | 5.96 ± 2.03 |
| Ca x P product | 51.87 ± 16.38 |
| ALP | 84.78 ± 39.65 |
| Vitamin D3 | 29.02 ± 12.25 |
| Intact PTH | 266.6 ± 270.2 |

(age group of 60 or above). Out of 71 patients, 66 (92.9%) were hypertensive and 26 (36.6%) were diabetic. Twenty-two (30.9%) patients had CVD at baseline. CAD was present in 20 (28.1%) patients, cerebrovascular disease was present in 2 (2.8%) patients and PAD was present in only 1 patient at baseline. Average dialysis duration received by patients was 21.35 ± 21.17 months. Out of 71 patients, 16 (22.5%) received calcium-containing phosphate binder, 51 (71.8%) received noncalcium-containing phosphate binder and 4 patients received no phosphate binder. Fifty-five (77.4%) patients received therapeutic or prophylactic vitamin D3 therapy during the study period.

## Prevalence of Vascular Calcification

- **Age:** Prevalence of vascular calcification (calcification score of ≥1) was 56.3%, which increased with increasing age of patients, for example, prevalence of vascular calcification was 60.4% in patients aged 60 years or above, whereas prevalence of vascular calcification was 50% in patients below 60 years of age. Severity of vascular calcification also increased with age, for example, 39.5% of patients above 60 years of age had vascular calcification score of 4 or above, whereas only 28.5% of patients between 40 to 60 years of age had vascular calcification score of 4 or above (Fig. 3).
- **Sex:** Prevalence of vascular calcification was similar in male and female patients. Out of 45 male patients, 25 (55.5%) had vascular calcifications and out of 26 female patients, 15 (57.6%) had vascular calcification.
- **Diabetes:** Prevalence of vascular calcification was significantly higher in hemodialysis patients who were diabetic (92.3%) compared to nondiabetic (35.5%) patients ($p < 0.0005$).
- **Hypertension:** Out of 66 hypertensive patients, 37 (56%) had vascular calcifications ranging from total vascular calcifications score of 1 to 8, whereas out of 5 normotensive patients, 3 (60%) had vascular calcification ($p = 0.864$).
- **CVD at baseline:** Out of 71 patients, there were 22 patients with CVD at baseline. Vascular calcification was present in 63.5% of patients with CVD at baseline, whereas it was present in 53% of patients without CVD at baseline ($p = 0.406$).
- **CAD at baseline:** Vascular calcification was more common in patients who had CAD at baseline compared to those who had no CAD at baseline (60% vs. 54.9%; $p = 0.009$). Moreover, among patients who had vascular calcifications, 30% had CAD at baseline compared to 25.8% in those with no vascular calcification (Table 2).
- **Cerebrovascular disease at baseline:** Only 2 patients had cerebrovascular disease at baseline and both the patients had vascular calcifications ($p = 0.589$).
- **Peripheral vascular disease at baseline:** Out of 71 patients, only 1 patient had peripheral vascular disease at baseline and vascular calcification was present in that patient ($p = 0.896$).
- **Hemodialysis duration:** Vascular calcification was present in 63.6% of patients on hemodialysis for 1 year or above at enrollment, whereas it was present

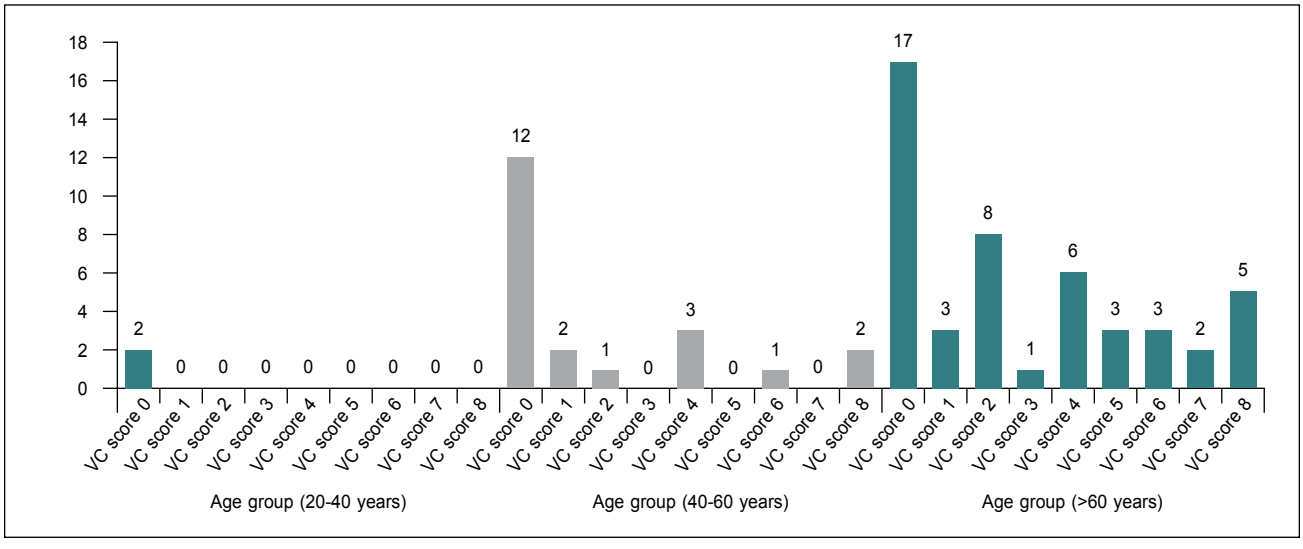


**Figure 3.** Vascular calcification score in different age groups.

VC = Vascular calcification.

**Table 2.** Vascular Calcification Score in Patients With and Without CAD at Baseline

| CAD (at baseline) | Vascular calcification score | | | P value |
|---|---|---|---|---|
| | 0 | 1-4 | 4-8 | |
| Yes (n = 20) | 8 (40%) | 3 (15%) | 9 (45%) | 0.009 |
| No (n = 51) | 23 (45%) | 21 (41.1%) | 7 (13.7%) | |

in only 44.4% of patients who were on hemodialysis for less than 1 year. However, this difference was not statistically significant (p = 0.113).

- **Serum calcium level:** Mean corrected serum calcium level was 8.33 ± 0.79. All the values were within the range of 7.2 mg/dL to 12.1 mg/dL. Majority of patients (n = 67) had normal or slight lower serum calcium levels, only 4 patients had hypercalcemia. Serum calcium level was not associated with vascular calcification (p = 0.193).
- **Serum phosphate levels:** Mean serum phosphorus level was 5.96 ± 2.03 mg/dL. Only 21 patients had achieved serum phosphorus levels within normal range meeting the recent KDIGO guidelines, out of which 14 had vascular calcifications, whereas 50 patients had serum phosphorus above the normal range, out of whom 26 had vascular calcifications. Therefore, hyperphosphatemia was not associated with presence of vascular calcification (p = 0.255).
- **Calcium-phosphate product:** Mean Ca x P product was 51.87 ± 16.38. In patients with Ca x P product >50, 54% had vascular calcifications whereas in patients with Ca x P product <50, 58.8% had vascular calcifications. Therefore, high Ca x P product does not appear to contribute to vascular calcification (p value 0.685).
- **Serum vitamin D3 levels:** Mean serum vitamin D3 level was 29.02 ± 12.25. Majority of patients (n = 43) had vitamin D3 levels ≤30, and 28 patients had vitamin D3 levels >30. There was no significant difference in prevalence of vascular calcification between the two groups base on vitamin D3 levels (p = 0.548).
- **Serum intact PTH:** Mean serum intact PTH levels was 266.6 ± 270.228 pg/mL. Thirteen patients had intact PTH levels below 150 pg/mL and 21 patients had intact PTH levels above 300 pg/mL, whereas only 22 (30.9%) met KDOQI guidelines for PTH (150-300 pg/mL). Paradoxically vascular calcification was most commonly (68.1%) seen in this group (p = 0.304).
- **Phosphate binder used:** Out of 71 patients, 16 patients were receiving calcium-containing phosphate binder and 51 were receiving non-calcium-containing phosphate binders. Around 62.5% patients on calcium-containing phosphate binders had vascular calcification, whereas 50.9% of patients on noncalcium-containing phosphate binders had vascular calcification. Therefore, vascular calcification was more common in patients taking calcium-containing phosphate binders, however, this difference was not statistically significant (p = 0.42).
- **Vitamin D therapy:** Out of 71 patients included in the study, 55 received prophylactic or therapeutic doses of vitamin D3 and among these patients, 34 (61.8%) had vascular calcifications whereas only 6 (37.4%) out of 16 patients not receiving vitamin D3, had vascular calcifications. Therefore, vascular calcification was more common in patients on vitamin D therapy; however, this difference was not statistically significant (p = 0.084).

### Vascular Disease Events During 1-year Follow-up

Total number of vascular disease (CAD, cerebrovascular disease, PAD) events that occurred over a follow-up period of 12 months were 9 and all events occurred in patients who had vascular calcification score ≥1 at the time of enrollment in the study (p = 0.013). Out of the total number of patients included in the study, 30.9% had CVD at baseline, which increased to 38% at the end of the study. However, in patients with vascular calcification, 35% had CVD at the time of enrollment, which increased to 47.5% at the end of the study.

### Cardiovascular Deaths During 1-year Follow-up

During the 1 year follow-up, out of 40 patients who had vascular calcifications, 1 patient died of a cardiovascular cause (p = 0.896). No deaths occurred in the patient group who had no vascular calcifications.

### All-cause Deaths During 1-year Follow-up

Out of 71 patients enrolled in the study, there were 6 deaths over a follow-up period of 1 year. All the deaths occurred in patients with vascular calcification. No death was reported in the patient group with no vascular calcifications (p = 0.068).

### New CAD Events Over 1-year Follow-up

There were 5 new CAD events over 1-year follow-up; all the events occurred in patients who had vascular calcifications at the time of inclusion in the study.

No new coronary event occurred in patients without vascular calcifications (p = 0.115). No cerebrovascular event (stroke, TIA) occurred in either group. However, two new peripheral vascular disease events occurred in the vascular calcification group, whereas no new peripheral vascular disease event was noted in patients with no vascular calcification.

New vascular events were more common in patients with total vascular calcification score of ≥4 compared to those with vascular calcification score <4. However, the difference was not statistically significant (p value 0.32).

There were 6 all-cause deaths, 4 in patients with total vascular calcification score of ≥4 and 2 in patients with score of <4. There was only 1 death due to cardiovascular-cause and that occurred in the patient with total vascular calcification score of ≥4 (p = 0.215).

## DISCUSSION

Vascular (medial) calcification is an active process that occurs due to failure of inhibitory mechanisms for calcification within VSMCs and differentiation of VSMCs into osteoblast-like cells. This type of vascular calcification is seen as railroad pattern on a plain radiograph.[18]

In this study, vascular calcifications were deliberately evaluated only in muscular arteries: iliac, femoral, radial and digital, because muscular arteries are more prone to linear calcification in contrast with elastic arteries that are more prone to intimal calcification. Vascular calcification causes arterial wall stiffness,[19] which results in increased cardiac afterload leading to left ventricular hypertrophy. These functional and structural changes associated with vascular calcification have strong clinical impact on cardiovascular morbidity and mortality in dialysis patients. Also, if the prevalence of both vascular calcification and CVD is high in hemodialysis patients, the association between the two observations seems logical. Indeed, several observational studies confirmed this association, suggesting linear relationship between vascular calcification and cardiovascular morbidity and mortality.[14,20-22]

The prevalence of vascular calcifications among patients with CKD especially those on dialysis is very high. Kraus et al found a prevalence of abdominal aortic calcification of 77.8%, on lateral lumbar X-rays in ESRD patients on hemodialysis.[20] Using plain radiograph of pelvis and wrists, Adragao et al found a prevalence of 74.7%.[18] However, prevalence of vascular calcification in patients on hemodialysis is found to be >80%, using EBCT.[5]

In this study, prevalence of vascular calcification detected with plain X-ray of pelvis and both wrists, was 56.3% which is lower than observed in other studies as discussed. Higher mean age of patients and longer dialysis duration could be the reasons for higher prevalence of vascular calcification in these studies. Older age is considered one among the major risk factors for vascular calcification, which was demonstrated in a comprehensive review of 30 studies over a period of 20 years; it showed that age and dialysis duration were the main factors associated with vascular calcification among hemodialysis patients.[10] Older age was associated with vascular calcification in other studies as well.[23,24] In our study, prevalence of vascular calcification was 60.4% in patients aged 60 years or above, whereas it was 50% in patients below 60 years of age. Severity of vascular calcification also increased with age confirming the findings of above studies. In this study, prevalence of vascular calcification was found to be significantly higher in patients with diabetes. These findings are consistent with the study published in 2003 by London et al.[16]

The Dallas Heart Study in 2005 demonstrated that CKD is associated with increased coronary artery calcification score but this association may be substantially stronger among patients with diabetes.[25] However, abdominal aortic calcification did not differ by diabetes status in another study, perhaps because fewer than 20% patients had diabetic nephropathy.[20] In this study, vascular calcification did not correlate with blood pressure, which is consistent with another study in which no association was found between vascular calcification and hypertension;[16] hypertension is considered a risk factor for atherosclerosis and not for vascular calcification. Vascular calcification was not significantly associated with overall CVD present at the time of enrollment in the study, which is consistent with the study by Adragao et al, in which clinical vascular disease diagnosed at baseline did not correlate with vascular calcification score.[18] Vascular calcification was more common in patients who had CAD (prior myocardial infarction [MI], CABG or coronary angioplasty/stenting) present at baseline compared to those with no CAD at baseline. This was in line with other studies, in which the patients with prior evidence of ischemic heart disease and dysrhythmia had increased abdominal aortic calcification.[20,24]

In another study in hemodialysis recipients, coronary artery calcification was related to prevalent MI and angina and aortic calcification was related to prevalent PAD.[26] The vascular calcifications may be present in

patients when RRT is started.[27] However, vascular calcification could be expected to increase with dialysis duration. In the study of Goldsmith and colleagues, in patients on hemodialysis for 10 to 25 years, radiographic vascular calcification prevalence increased from 39% at dialysis onset to 92% after an average dialysis duration of 16 years, with a mean onset 9.7 years after starting dialysis;[12] calcification severity also increased with age. Another study also showed that the prevalence and progression of vascular calcification increases once patients are on dialysis.[28] Similarly, in CORD study, dialysis duration independently predicted abdominal aortic calcification on multivariate analysis.[24]

In the current study, vascular calcification did not increase with dialysis vintage, perhaps due to shorter mean dialysis duration in our patients compared to above studies. This finding is also consistent with the results of another study in which the overall abdominal aortic calcification score did not increase with dialysis duration.[20] Most experts believe that a raised plasma phosphate and calcium level leads to the initiation and progression of vascular calcification.[11] However, vascular calcification was not correlated with serum calcium, serum phosphorus and intact PTH levels in our study. Similarly, Guérin et al did not find any association between a semiquantitative vascular calcification score evaluated by B-mode ultrasonography and calcium, phosphorus and intact PTH levels.[17] Final vascular calcification score was also not correlated with serum calcium, phosphorus and intact PTH in the study done by Adragao et al.[18] Majority of hemodialysis patients are vitamin D deficient and receive therapeutic or prophylactic doses of vitamin D3. In our study, serum level of 25(OH)D3 was not associated with the vascular calcification, as also reported by London et al.[29]

However, in another study of vascular calcification in hemodialysis patients, levels of vitamin D metabolites correlated with the extent and progression of vascular calcifications.[12] Vascular calcification was not associated with vitamin D therapy in our study, probably, because majority of our patients received prophylactic doses of vitamin D3 rather than therapeutic doses that might increase the risk of hypercalcemia, Ca x P product which could increase the chances of vascular calcification. Noncalcium-containing phosphate binders have been associated with delayed progression of vascular calcification compared with calcium-containing phosphate binders. This was demonstrated by several studies.[30-32]

In this study, vascular calcification was more common in patients taking calcium-containing phosphate binders compared to those taking noncalcium-containing phosphate binder; however, this difference was not statistically significant. However, the CARE-2 trial did not find a difference in progression of coronary artery calcification with sevelamer and calcium acetate.[33] Also, a meta-analysis that analyzed 14 researches could not find sevelamer hydrochloride more effective than calcium-based phosphate binders for delaying the progression of coronary artery calcification.[34] Cardiovascular calcification predicts future cardiovascular morbidity and mortality in general population and dialysis patients. In the prospective general-public Framingham Heart Study with 22 years of follow-up, vascular calcification was associated with increased relative risk of CVD, coronary heart disease and cardiovascular mortality.[35] Several studies have also demonstrated association between vascular calcification and cardiovascular morbidity and mortality, and all-cause mortality in hemodialysis patients.[21,22,36-38] The number of calcified sites was a strong predictor of cardiovascular and all-cause mortality.[14] Importantly, the associations found in these studies persisted after correcting for established risk factors. Moreover, longitudinal studies revealed that the progression rate of vascular calcification is also associated with the incidence of subsequent cardiovascular complications.[39] In the present study, vascular disease events at the end of the follow-up was strongly associated with the presence of vascular calcification, which is consistent with other 54 studies.[18,39]

However, unlike the above study, total vascular calcification score was not an independent predictor of cardiovascular events, cardiovascular mortality and all-cause mortality in our study. In this study, presence of vascular calcification and total calcification score did not correlate with cardiovascular and all-cause mortality, which is not consistent with other studies,[21,40,41] the likely reason could be the shorter follow-up period in our study. However, higher peripheral vascular calcification on X-rays was associated with increased mortality rate in 161 French hemodialysis patients followed over a period of 1 year;[23] the mean age of patients was higher, with longer dialysis duration in this study. PAD is highly prevalent in hemodialysis patients, but is often underdiagnosed. The risk factors such as age and diabetes, hypercalcemia and hyperphosphatemia have been associated with higher risk of amputation suggesting a contributory role of vascular calcifications for PAD in this population.[42,43] Furthermore, lower limb arterial calcification is closely associated with the presence and severity of PAD in hemodialysis patients.[43] This was

also confirmed by another study in which vascular calcification score was independently associated with PAD at the end of follow-up.[18]

However, this study did not show correlation between vascular calcification and peripheral vascular disease at the end of follow-up, likely because of shorter follow-up and smaller sample size.

## CONCLUSIONS

There was a high prevalence of vascular calcification in maintenance hemodialysis patients in our center. There is a need to sensitize clinicians towards the high risk of vascular calcification in CKD population. The risk factors of vascular calcification are higher age, diabetes and CAD. These patients should be followed-up regularly for vascular events. We also want to reiterate with this study that plain X-ray of pelvis and wrists are sufficient to rule out vascular calcification in CKD patients and should be employed regularly in dialysis clinics.

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CASE REPORT

# An Interesting Endocrine Cause of Pyrexia of Unknown Origin: A Case Report and Review of Literature

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## ABSTRACT

Pyrexia of unknown origin (PUO) is one of the most challenging medical problems. Endocrine causes of PUO are rare. Fever is common in a few endocrine disorders (e.g., thyroid storm, adrenal crisis and pheochromocytoma). However, PUO as the sole presenting feature is very rare with only a few reported cases in the literature. We present the case of a middle-aged male who came to us with PUO, weight loss and loss of appetite. The unusual symptomatology like loss of appetite, altered bowel habits made diagnosis difficult. This case highlights the importance of considering thyroid disorder in the differential diagnosis of PUO. Abnormal thyroid function may be an early clue for diagnosis.

**Keywords:** Pyrexia of unknown origin, hyperthyroidism, endocrine disorders

Pyrexia of unknown origin (PUO) is one of the most challenging medical problems. Most common causes include infections, malignancy and autoimmune disorders. Endocrine causes of PUO are rare. Fever is common in a few endocrine disorders (e.g., thyroid storm, adrenal crisis and pheochromocytoma). However, PUO as the sole presenting feature is very rare with only a few reported cases in the literature.[1,2] We present a case of hyperthyroidism presenting with PUO. The patient did not exhibit any classic thyroid symptoms at the time of presentation. Therefore, a thyroid disorder was not suspected initially. This unusual presentation of a common medical problem highlights the importance of considering a thyroid disorder in the differential diagnosis of PUO.

## CASE DETAILS

A 52-year-old male patient, who was a known case of diabetes mellitus for 10 years on oral hypoglycemic agents, presented with complaints of loss of appetite and loss of weight for 2 months. He had lost ~12 kg in 2 months. He also had on and off low-grade fever with associated night sweats for 6 weeks along with altered bowel and bladder habits and increased frequency of urine.

On physical examination, he was moderately built and poorly nourished with height of 178 cm, weight of 69 kg, body mass index (BMI) of 21.78 kg/m$^2$ and body surface area (BSA): 1.85 m$^2$. He was afebrile and his pulse rate was 120/min with regular rhythm, normal volume, no radial - radial delay, with normal vessel wall, and all peripheral pulses well felt. His blood pressure was 100/70 mmHg. Systemic examination was unremarkable. Baseline investigations revealed hemoglobin (Hb) - 11.3 g/dL, total leukocyte count (TLC) - 9.4, differential leukocyte count (DLC) - ($N_{74}L_{15}E_0M_{11}$), platelet - 2,26,000 cells/mm$^3$. His erythrocyte sedimentation rate (ESR) was 80 mm in the first hour. Peripheral blood smear showed normochromic normocytic cells with moderate rouleaux formation. The blood biochemistry was as follows: blood glucose (random) - 144, urea - 31, creatinine - 0.7, HbA1c - 7.7%, total bilirubin - 0.6 mg/dL (0.3/0.3), total protein - 9.1, albumin - 4, globulin - 5.1, A:G = 0.78, aspartate transaminase/alanine transaminase (AST/ALT) - 84/132, gamma-glutamyl transpeptidase (GGTP) - 69, alkaline phosphatase (ALP) - 99. Urine routine examination showed glucosuria (3+), ketonuria (1+) with no RBCs or pus cells.

Two sets of blood cultures and urine culture were sterile. In two-dimensional echocardiogram, the valves and the endocardium were free of vegetations. Human

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immunodeficiency virus (HIV) ELISA (enzyme-linked immunosorbent assay) test was negative. 640-slice CT chest and abdomen were done; both were noncontributory. Bone marrow biopsy was done. Aspiration cytology showed hypercellular marrow with trilineage hematopoiesis and erythroid hyperplasia. Histopathological examination confirmed variably cellular marrow with trilineage hematopoiesis and was negative for focal lesions. Xpert MTB test for tuberculosis was negative and culture was sterile.

$^{18}$F-fluorodeoxyglucose (FDG)-avid ill-defined hypodense nodule in the lower pole of left lobe of thyroid was found on positron emission tomography-computed tomography (PET-CT) whole body with no other significant metabolically active disease. Thyroid-stimulating hormone (TSH) was <0.01 and free thyroxine (T4) was 2.5. Antithyroid peroxidase (2.83) was negative and anti-triglyceride (9.1) was positive as per thyroid antibody profile. He was started on carbimazole 5 mg twice daily and was reviewed after 3 months. His fever settled, appetite improved and there was 5 kg increase in weight since commencement of treatment.

## DISCUSSION

Hormones play an important role in thermoregulation. Various endocrine disorders like thyroiditis, hyperthyroidism, Addison's disease, pheochromocytoma, primary hyperparathyroidism and hypoglycemia can produce fever.[3,4] Fever is one of the common symptoms in patients with subacute thyroiditis (SAT)[5,6] and thyroid crisis,[7,8] but the manifestation of thyroid disease as fever alone is very rare. Prolonged fever as the only manifestation of SAT has been reported previously. SAT follows a triphasic course of thyrotoxicosis, hypothyroidism and subsequent restoration of euthyroidism in most of the patient. Rarely, hyperthyroidism can manifest with persistent fever for many months without clinical symptoms or signs to lead to suspicion of thyroid disease, which may become evident only after exhaustive investigation.[9] While we generally see normal appetite in patients with hyperthyroidism, our patient has significant loss of appetite which we generally see in hypothyroidism, which made diagnosis challenging.

The pathogenesis of fever in thyrotoxicosis is not completely understood yet. Although, thyroid hormone is known to be calorigenic, the precise mechanism for this thermogenesis is still debated, and is widely believed to be due to stimulation of the membrane-bound sodium-potassium ATPase (sodium pump).[10] Heat intolerance and an increased basal metabolic rate are common in hyperthyroidism. The true incidence and grade of fever in uncomplicated hyperthyroidism has not been determined and, if present, is usually of low-grade in most patients. A study by Pala et al revealed that, out of 25 patients, 20 (80%) had SAT and 5 (20%) had hyperthyroidism. Patients with hyperthyroidism received thionamides and β-blockers. Fifty percent patients with SAT received analgesics, 25% received steroids only and 25% received a combination of analgesics and steroids. Early-onset transient hypothyroidism occurred in 40% patients with SAT; permanent hypothyroidism was less common and only 15% of patients were receiving levothyroxine therapy after 1 year of follow-up.[11] Our patient was started on antithyroid medications (carbimazole) following which his fever settled and he regained his appetite and gained weight significantly.

## CONCLUSION

Endocrine disorders could be one of the rare causes of PUO. Hyperthyroidism should be considered in the differential diagnosis even if clinical symptoms of thyrotoxicosis are not present. Abnormal thyroid function may be an early clue for diagnosis.

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CASE REPORT

# A Rare Case of an Intratonsillar Abscess

S VINAYAK EASWERAN*, PADMINI BHIMSEN†, MAMTA HEGDE‡

## ABSTRACT

The case describes the anatomy and pathophysiology of the palatine tonsils and the development of intratonsillar abscess. The abscess can be caused by a suppurative focus that arises in acute tonsillitis when outward drainage is prevented, leading to pus accumulation in the tonsillar tissue. Dehydration or a history of peritonsillar abscess can also lead to intratonsillar abscess. The condition can be mistaken for tonsillolith or malignancy, such as lymphoma. A computed tomography (CT) scan is recommended for diagnosis, showing a low-density and ring enhancement. Aspiration using a large bore needle is the preferred mode of treatment, but if repeated aspirations fail, tonsillectomy may be necessary. Intratonsillar abscess is rare and so far only 29 cases have been reported.[1] The differential diagnoses include lymphoma, which usually presents as unilateral enlargement of the tonsil, tonsillolith due to its appearance and peritonsillar abscess again due to the unilateral enlargement of the tonsil. This case is different as compared to other reported cases we did not do a CT scan as recommended by most of the studies (cost being a concern). Also, in this case, we resorted to surgery as the main modality unlike other cases wherein the surgeons opted to do an aspiration of the pus mainly keeping the intraoperative complications in mind.

**Keywords:** Intratonsillar abscess, chronic tonsillitis, quinsy, aspiration, tonsillectomy

Intratonsillar abscess is a condition which is rarely seen in the practice of an ENT surgeon. It is also diagnosed less often. It is formed in the parenchyma of the tonsil. Clinically, intratonsillar abscess may mimic chronic tonsillitis or quinsy (peritonsillar abscess). Tonsillitis, which usually affects children and rarely young adults, is a commonly seen entity in ENT outpatient departments (OPDs). Treatment options include antibiotics, incision and drainage and tonsillectomy.

## CASE REPORT

A 32-year-old male presented to the ENT OPD with enlargement of the left tonsil since 3 to 4 years with off and on increase in the size of the swelling coinciding with bouts of upper respiratory infections (URI) (Fig. 1). During the URI episodes, the patient also complained of odynophagia, halitosis and a raw sensation in the throat and fever. He relied on home remedies to get relief from these symptoms.

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After examination, he was prescribed capsule amoxicillin 500 mg 1-0-1, diclofenac sodium 1-0-1, tablet paracetamol 1-0-1, tablet ranitidine 1-0-1 on an empty stomach and a povidone-iodine based mouth gargles for a week so that the acute bout subsided.

Follow-up examination after 10 days revealed that the left tonsil including the yellowish growth on the upper pole of the same tonsil had not regressed in size.

He was advised to undergo bilateral tonsillectomy keeping lymphoma as a probable diagnosis in mind.

Prior to tonsillectomy his blood and urine were sent for routine investigations, which were as follows: Hemoglobin was 14.2 g/dL, thyroid profile was within normal range, bleeding time and clotting time were also within normal limits, random blood sugar was 105 mg/dL and the reverse transcriptase polymerase chain reaction (RT-PCR)

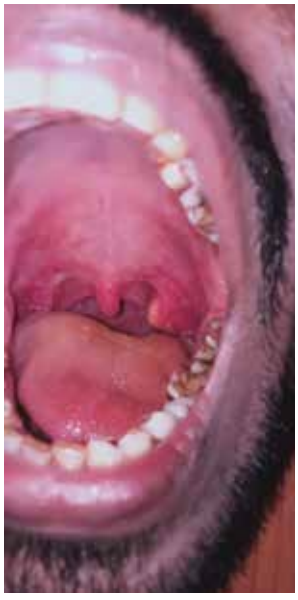

**Figure 1.** Patient's intraoral picture showing enlarged tonsil on the left side with a prominent yellowish growth on upper pole of tonsil.

**Figure 2.** Gross picture of left-sided tonsil with pus within the tissue measuring 2.5×1.5×1 cm.

**Figure 3.** Cut section shows yellowish fluid filled within cystic cavity.

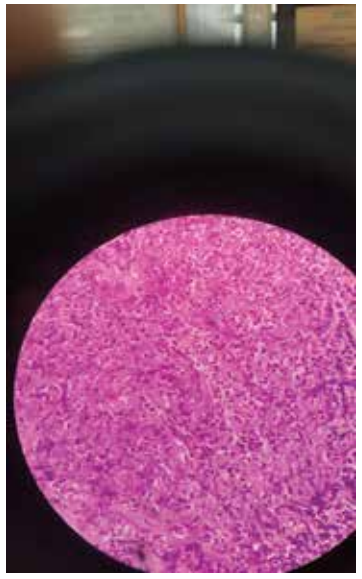

**Figure 4.** Microscopic picture showing numerous neutrophils.

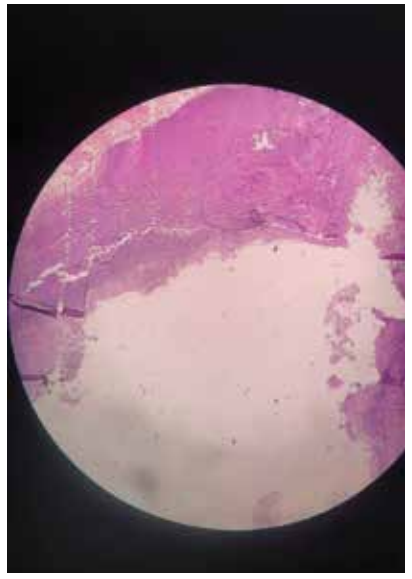

**Figure 5.** Cut section of left tonsil showing tonsillar tissue composed of lymphoid tissue lined by stratified squamous epithelium and cavity lined by inflammatory cells mainly neutrophils, lymphocytes, plasma cells and macrophages.

test for COVID-19 was negative. The patient underwent bilateral tonsillectomy under general anesthesia.

Post-tonsillectomy, the tonsils were sent for histopathological examination.

The gross pictures of the specimen as shown in Figures 2 and 3 were rather surprising as they showed pus in the tonsil parenchyma, which went in favor of diagnosis of "intratonsillar abscess", and the microscopic findings too confirmed the diagnosis of "intratonsillar abscess" (Figs. 4 and 5).

## DISCUSSION

The palatine tonsils are a part of the Waldeyer's lymphatic ring. They are located between the palatoglossal muscles anteriorly, palatopharyngeus muscle posteriorly and superior pharyngeal constrictor muscle laterally.

The tonsils are covered by fibrous sheath of connective tissue and nonkeratinized squamous epithelium. Tonsils have crypts in their structure, the largest crypt is magna crypta or intratonsillar cleft.

The superior pharyngeal constrictor helps in the contraction of the tonsillopharyngeus muscle facilitating the expulsion of the crypt contents.

Michaels and Hellquist[2] suggested that when and if a suppurative focus arises in a case of acute tonsillitis and the outward drainage is prevented; a block in the crypt causes the pus to go inwards leading to an intratonsillar abscess.

The low incidence of intratonsillar abscess is due to the absence of lymphatic valves[3] prior to the capsule, which does not allow aggregation of bacteria in the tonsillar tissue. Therefore, conditions affecting lymphatic flow such as dehydration or a previous history of peritonsillar abscess could lead to intratonsillar abscess.

Due to its gross appearance, an intratonsillar abscess could be mistaken for a tonsillolith.

As the abscess causes unilateral tonsillar enlargement, malignancy should be kept in mind, most commonly lymphoma.

Misdiagnosis of an intratonsillar abscess may lead to overuse of antibiotics leading to risk of antibiotic resistance.

Although a computed tomography (CT) scan is usually recommended for cases of intratonsillar abscess, it was not performed in this particular case because the differential diagnosis did not require it. However, a CT scan can be helpful in diagnosing an intratonsillar abscess as it would reveal a low-density and ring enhancement.

Management of any abscess requires early drainage. The preferred mode of treatment according to most

studies is aspiration using a large bore needle, but needle aspiration requires repeated sittings and more importantly, the patient's cooperation.

Review of medical literature reveals that few patients after repeated aspirations underwent tonsillectomy,[5] which was also done in our case.

## CONCLUSION

Intratonsillar abscess is a rare condition, and an accurate diagnosis can be challenging for otorhinolaryngologists.

In this particular case, a CT scan was not advised for the patient as the differential diagnosis did not warrant it. The patient underwent tonsillectomy as a treatment modality, although aspiration is also a viable treatment option if the patient is compliant with the procedure. As with any medical condition, careful consideration of the patient's individual circumstances and medical history is necessary to determine the best course of treatment.

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■■■■

### Critical Vis-à-Vis Severe H1N1 Pneumonia

Patients with critical H1N1 pneumonia have more diffuse involvement of both lungs with greater prevalence of consolidation compared to patients with severe illness, according to a study published in the April 2023 issue of the *Clinical Respiratory Journal*.[1] The number of lobes affected was also higher in critical patients with more frequent involvement of the middle lobe.

To analyze the clinical and radiological differences between severe and critical illness, 27 patients who had been diagnosed with H1N1 pneumonia between October 2018 and March 2019 were enrolled in this retrospective study. Fifteen patients had severe pneumonia and 12 had critical pneumonia.

Patients with more than 3 days of high fever (>38.5°C) with severe cough with purulent or bloody sputum/chest pain; tachypnea, dyspnea and cyanosis; dull reaction, hypersomnia, and restlessness; severe vomiting, diarrhea and dehydration; pneumonia and significant worsening of underlying disease were categorized as severely ill. Patients with respiratory failure, septic shock, multiorgan failure were considered as critical cases. When the differences in clinical manifestations and laboratory parameters were analyzed, dyspnea at rest was found to be more common in the critical patients than in the severe patients. The critical group also had higher neutrophil and lower lymphocyte percentages. On imaging, both critically and severely patients had bilateral involvement of the lungs, although the number of lobes that were affected was higher in the critical group (vs. severe group). Middle lobe involvement was significantly higher in the critical group (~92%) than in the severe group (~27%). Involvement of lungs was more diffuse in the critical group (83.30%), while the severe group had more peripheral involvement (40%).

Both groups of patients had ground-glass opacities and consolidation on chest CT. The prevalence of consolidation was higher in critical group versus severe group; 83.30% versus 33.3%, respectively. More critically ill patients had interlobular septal thickening but this difference was statistically nonsignificant. Both groups had comparable airway involvement, lymph node enlargement and pericardial effusion. This study shows that clinical features, lab results and chest CT scan findings can together distinguish between severe and critical H1N1 pneumonia. Early identification of critical illness enables timely interventions before it becomes unsalvageable.

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CASE REPORT

# Arrhythmia in Adult Congenital Heart Disease

DEVENDRA SINGH BISHT*, KAMAL KISHOR†, MOHIT JAIDKA‡

## ABSTRACT

This case report highlights the significance of a multidisciplinary approach in the management of patients with repaired membranous ventricular septal defect (VSD) who develop postoperative arrhythmias. We present the case of a young female who experienced symptomatic episodes of supraventricular tachycardia following VSD repair. Through electrophysiological study and radiofrequency ablation, multiple tachycardia substrates were identified and successfully ablated. This report underscores the importance of combining surgical repair, electrophysiological evaluation and intervention to achieve optimal outcomes in this specific patient population.

**Keywords:** Arrhythmia, adult congenital heart disease, electrophysiological study, radiofrequency ablation

Congenital heart disease (CHD) encompasses a wide spectrum of structural abnormalities affecting the cardiovascular system. Advances in medical and surgical interventions have significantly improved survival rates among individuals with CHD. However, the long-term consequences and associated complications of repaired CHD remain an ongoing challenge.

In this case report, we present a unique clinical scenario involving a patient with repaired ventricular septal defect (VSD) who presented with recurrent arrhythmias. The investigation of this case led to the identification of a multiple tachycardia substrate and coronary sinus diverticulum, a rare anatomical variant, as the underlying etiology for the arrhythmic manifestations. We describe the diagnostic and therapeutic interventions employed, which resulted in successful resolution of the patient's symptoms.

## CASE REPORT

A 17-year-old girl was referred to our arrhythmia center for electrophysiological study for recurrent paroxysmal episodes of regular palpitations. She had medical history of recently repaired VSD. Physical examination, transthoracic echocardiography (TTE) and biochemical tests were unremarkable. There was no family history of cardiac arrhythmia. Baseline electrocardiogram (ECG) showed sinus rhythm, pre-excited QRS with delta wave polarity suggestive of left posterior accessory pathway (Fig. 1).

After written informed consent, patient was taken for electrophysiological study. Two quadripolar diagnostic catheters were advanced under fluoroscopy to His bundle region and right ventricular apex. One decapolar catheter was advanced into the coronary sinus. During the electrophysiological study at baseline, atrial-His bundle (AH) and His-ventricular (HV) intervals were 85 ms and 3 ms in sinus rhythm, respectively. There were no atrioventricular (AV) conduction abnormalities. A narrow complex tachycardia (tachycardia cycle length [TCL] = 400 ms) was easily induced during catheter placement with following features: initiation of the tachycardia with a critical AH interval, fixed 1:1 ventriculoatrial (VA) conduction, concentric retrograde activation with VA interval of 37 ms, a post-pacing interval (PPI, 576 ms)–TCL (406 ms) >115 (170 ms) and ventricular overdrive pacing resulted in a VAHV response. His synchronized and early premature ventricular contraction (PVC) did not reset the tachycardia. His synchronized premature atrial contraction (PAC) also failed to reset the tachycardia. The tachycardia was reproducible and consistent (Fig. 2). After confirming the diagnosis of typical AV nodal re-entrant tachycardia (AVNRT) a decision was taken for slow pathway ablation. Using a steerable ablation catheter, with the help of intracardiac electrograms (EGMs) and using fluoroscopy, the region of the slow

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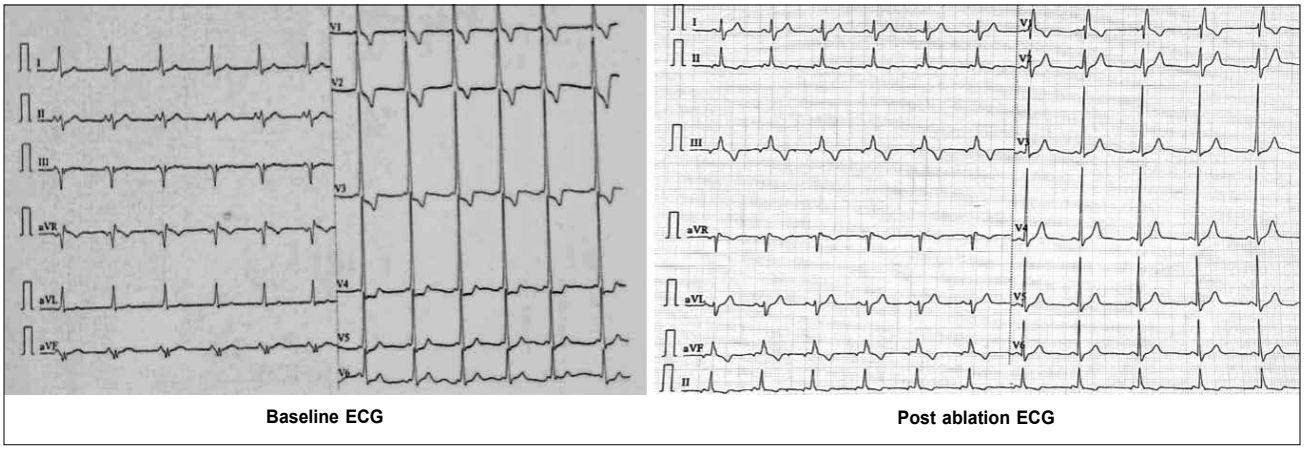


**Figure 1.** ECG (left) at baseline diagnostic of posteroseptal accessory pathway, ECG (right) after successful ablation of pathway with memory T waves in inferior leads.

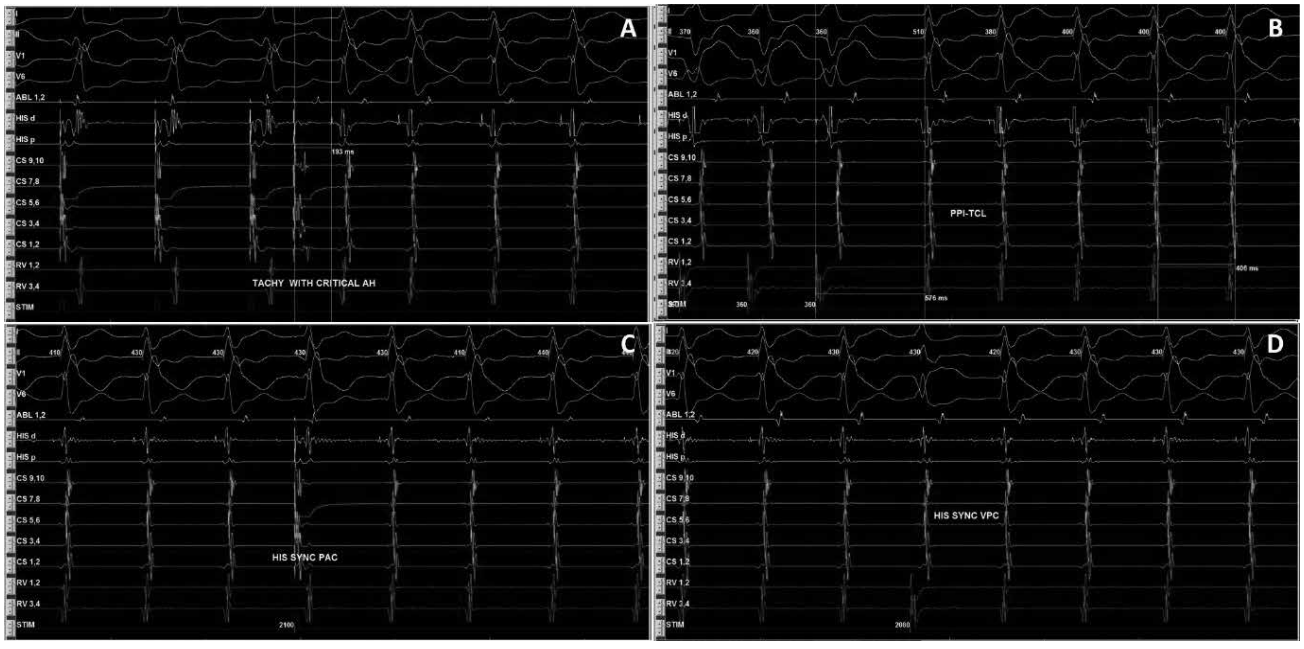


**Figure 2.** Intracardiac EGMs showing tachycardia induction with AH jump **(A)**, RV overdrive pacing **(B)**, and response of His synchronous PVCs **(C)** and PACs **(D)** diagnostic of typical slow-fast AVNRT.

pathway was identified. Radiofrequency applications were made in the region of the slow pathway while constantly monitoring temperature, impedance, ECG and intracardiac EGMs, monitoring for fast junctional conduction and radiofrequency energy was halted if there was evidence of VA block. Radiofrequency ablation resulted in a junctional rhythm with intact AV conduction, which is a typical response. The AV nodal slow pathway was successfully modified (Fig. 3).

Later on, during programmed atrial stimulation with burst pacing, patient developed another broad complex tachycardia (TCL = 220 ms) with 1:1 AV relationship. The tachycardia was hemodynamically unstable and led to ventricular fibrillation and required direct current cardioversion (DCCV) with 200J (Fig. 4). With the help of steerable ablation catheter, earliest atrial activation during ventricular pacing and earliest ventricular signal in sinus rhythm was mapped at the septal tricuspid annulus (RA mapping) and septal mitral annulus (LA mapping). Afterwards coronary sinus angiogram was taken, which showed a coronary sinus diverticulum near the decapolar coronary sinus 5-6 electrodes (Fig. 5). Radiofrequency applications were delivered at the neck of diverticulum that leads to disappearance of pre-excitation (Fig. 6). Afterwards aggressive programmed stimulation done on and off with isoproterenol that did not induce any atrial arrhythmias.

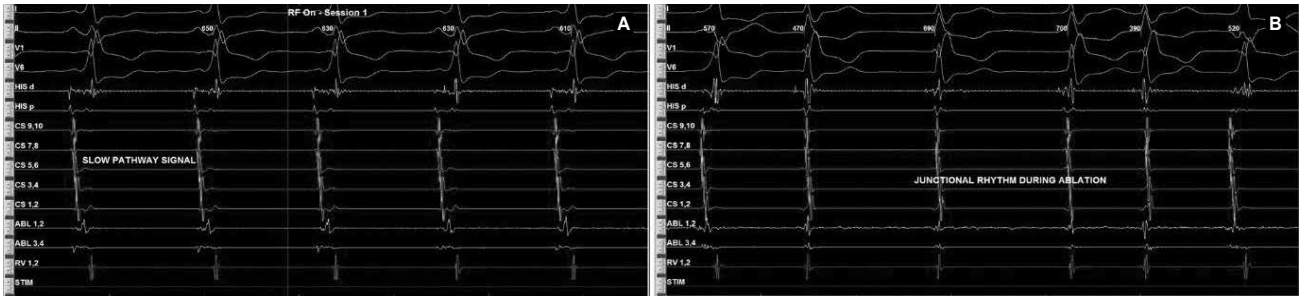


**Figure 3.** Slow pathway signals **(A)** at rightward inferior extension showed fused signals because of underlying pathway. Junctional rhythm **(B)** in response of radiofrequency energy.

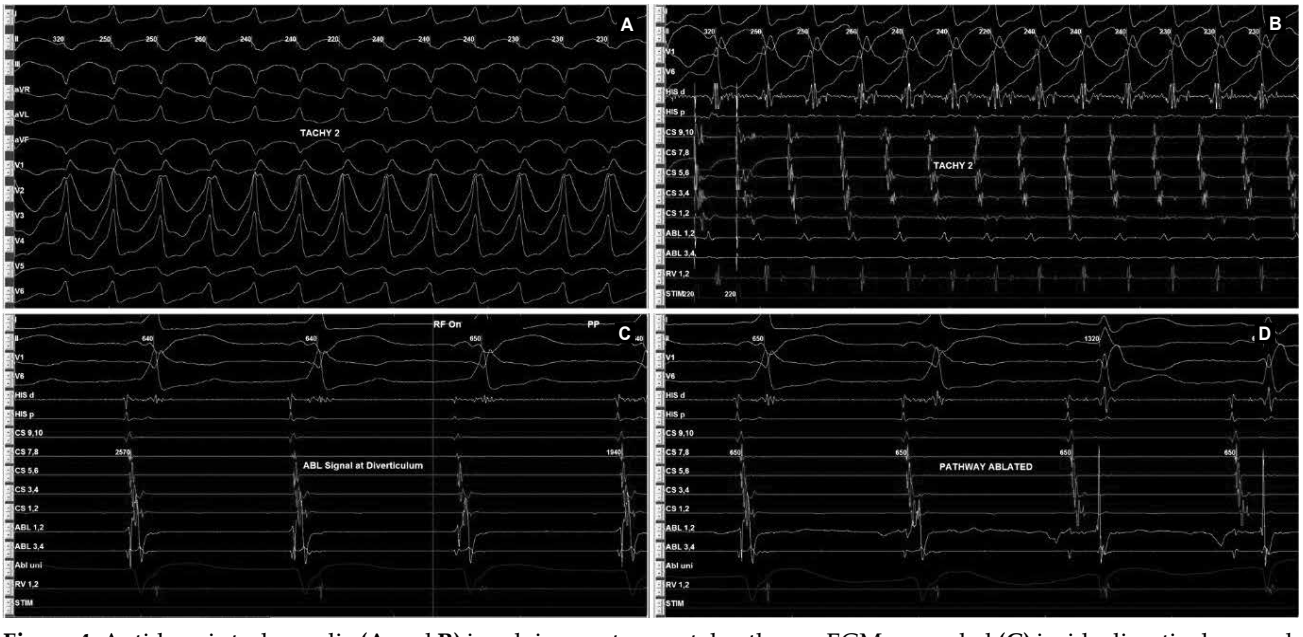


**Figure 4.** Antidromic tachycardia **(A** and **B)** involving posteroseptal pathway. EGMs recorded **(C)** inside diverticulum neck that was ablated successfully **(D)**.

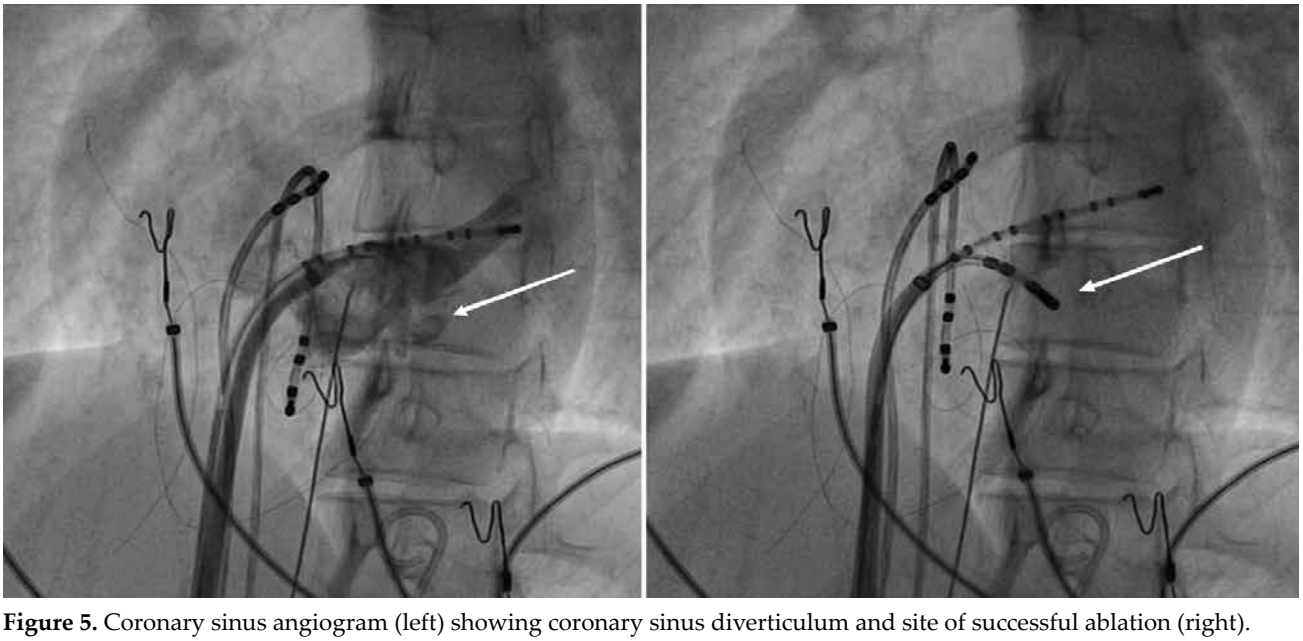

**Figure 5.** Coronary sinus angiogram (left) showing coronary sinus diverticulum and site of successful ablation (right).

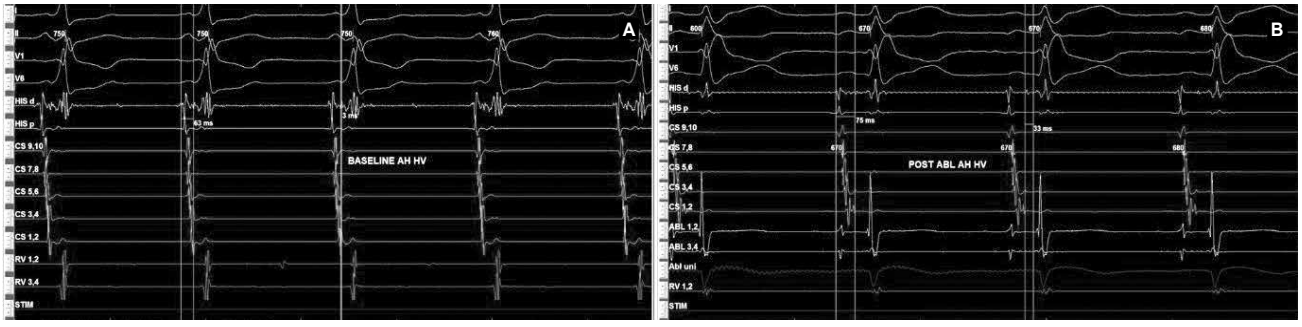


**Figure 6.** Intracardiac intervals baseline **(A)** showed HV interval of 3 ms that was normalized **(B)** after successful accessory pathway ablation.

During the follow-up, the patient remained free of symptoms and was not required to take antiarrhythmic agents. We did not find any conduction trouble on the ECG during the follow-up.

## DISCUSSION

Coronary sinus diverticula are rare congenital anomalies. These are venous pouches at the pericardial aspect of posterior ventricular septum with neck draining into the proximal coronary sinus. They also contain accessory pathway at the neck of diverticula. Radiofrequency catheter ablation appears to be safe and curative in this setting. These diverticulae may be associated with other congenital cardiac abnormalities like membranous VSD and subaortic membranes.[1-6]

Surgical series suggest they may be present in 6% to 9% of patients with posteroseptal accessory pathways with symptoms severe enough to warrant surgery.[7] In patients undergoing transesophageal echocardiography (TEE) following failed attempts at ablation of a posteroseptal accessory pathway, coronary sinus diverticulae were identified in 13% of cases. So, it is reasonable to do a coronary sinus venogram in case of posteroseptal or left posterior accessory pathway.

The posteroseptal accessory pathway is responsible for AV reciprocating tachycardia. Orthodromic re-entrant tachycardia mediated by posteroseptal pathway mimicking AVNRT, can be differentiated by different pacing maneuvers. However, the two may co-exist as seen in our case. Secondly, it is important to note that when accelerated junctional rhythm occurs during slow pathway ablation, the presence of retrograde atrial activation is reassuring, yet when a retrograde accessory pathway is present, the reassurance would be potentially false.

## CONCLUSION

It is important to predict the accessory pathway location from the delta wave polarity. In patients with left posterior and posteroseptal accessory pathways coronary sinus venogram is recommended to identify coronary venous anomaly. Multiple arrhythmias can co-exist, so one needs to identify all the possible substrates.

## Acknowledgment

We would like to acknowledge Mr Brijesh Yadav and Mr Mandeep Singh, Clinical Support, St. Jude Medical, Abbott India for their clinical assistance during the procedure.

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**Conflict of interest:** None.

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BRIEF COMMUNICATION

# Ghost of Medical Gaslighting

KAMAL KISHOR*, DEVENDRA SINGH BISHT†, SANJAY KALRA‡

## ABSTRACT

Medical gaslighting is when the actual symptoms of patients are dismissed or downplayed by medical professionals. It occurs frequently among patients suffering from chronic illnesses for which medical science gives no authoritative diagnostic protocol or effective treatment and those from populations underrepresented in clinical trials such as the female gender, specific races and ethnicity, third gender and patients with disability. Gaps in scientific knowledge and missing empathy have been cited as possible reasons. Respecting patient symptoms, accepting epistemic humility and investing in research may be possible solutions for this disharmony.

**Keywords:** Gaslight, medical professionals, factious, chronic illnesses, epistemic humility, missing empathy

## WHAT IS GASLIGHTING?

The word Gaslight originates from the title of a famous movie named Gaslight (1944), originally adapted from Patrick Hamilton's play Gaslight (1938).[1] The play depicts a deceitful husband who mysteriously dims the light of a gas lamp in the attic while assuring her wife that it is her perception only. With such subtle and disguised attempts, he wants to convince her wife that she is descending into insanity. Inspired by the play, Smith and Sinanan published an article titled "The Gaslight Phenomena". They documented how two victims were labeled mentally ill or demented by the accused to get rid of them from their living place.[2] Gaslighting in the above context refers to an act of psychological manipulation. However, the second and straightforward sense of gaslighting refers to grossly misleading someone, especially for one's advantage.[3] In recent years, gaslighting has become a favored word for the perception of deception, and this way, it is used in many contexts, which has contributed to it becoming Merriam-Webster's Word of the Year for 2022[3,4] (Fig. 1).

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## WHAT IS MEDICAL GASLIGHTING?

"Medical gaslighting" is an informal term used in case the actual symptoms of patients are dismissed or downplayed by medical professionals.[5,6] Patients' symptoms are dismissed as the product of their imagination leading to delays or errors in diagnoses. Thus, medical gaslighting may significantly impact longevity or quality of life.[7]

## POSSIBLE REASONS

As mentioned above, gaslighting results from contentious interactions with medical professionals when they dismiss patients' complaints as being factious. Nevertheless, why do medical professionals dismiss a person's health concerns?

Here we need to answer three questions:

### Is There Any Specific Patient Group Feeling Gaslighted More Frequently?

Medical gaslighting is frequent with two groups of patients. The first group comprises patients suffering from chronic illnesses, such as chronic fatigue syndrome, long COVID illness, migraine and fibromyalgia, for which medical science gives no authoritative diagnostic protocol or effective treatment.[8-11]

Medical science lacks objective tests to measure the intensity of symptoms in such diseases. Long and tiring diagnostic workups with no conclusive endpoints set a state of contentious interaction with medical professionals. Here patients feel that claims of their subjective "symptoms" are being denied without

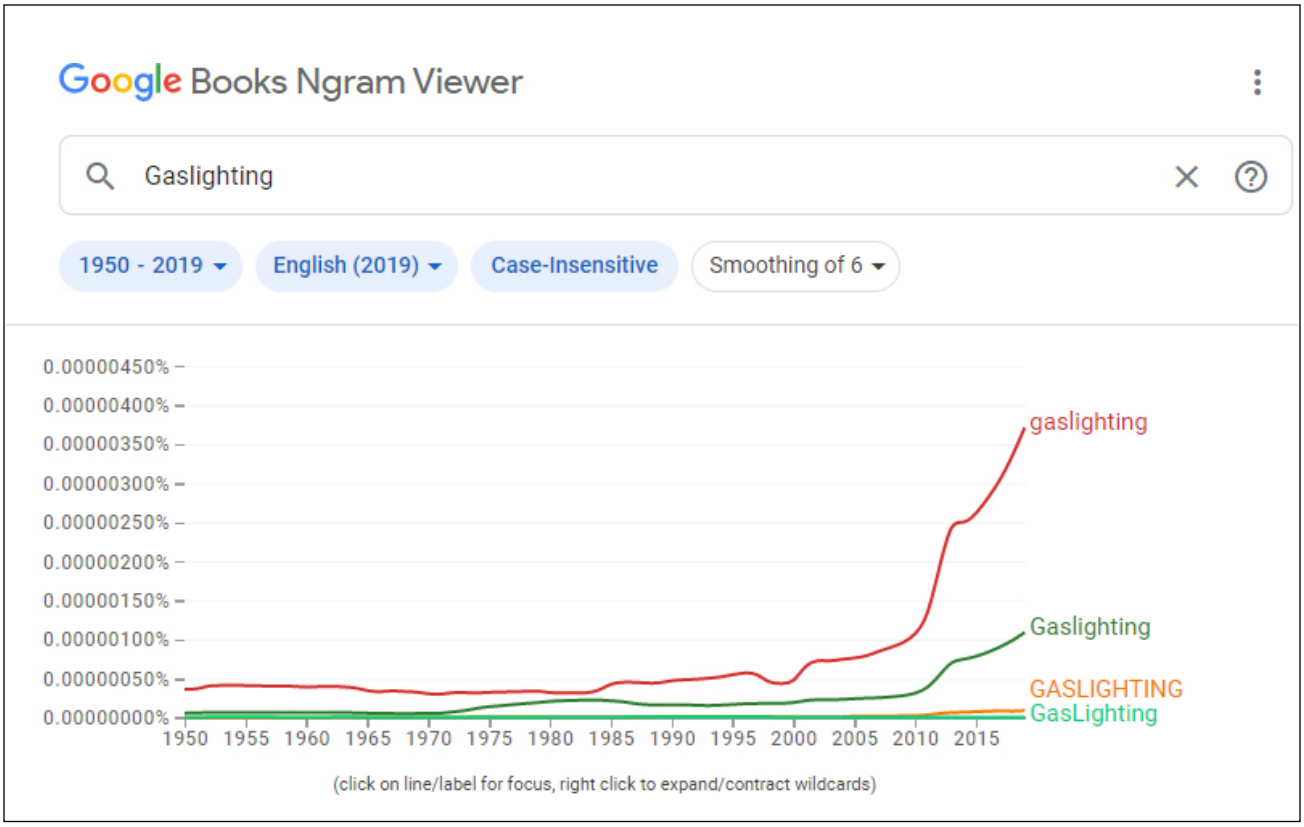


**Figure 1.** Recent surge in search 'Gaslighting' and words with similar meaning. [Adapted from GoogleBooks Ngram Viewer].

**Summary: Medical Gaslighting**

Medical Gaslighting reflects the state where a medical professional dismisses a person's health concerns as a product of their imagination.

**Possible Reasons**

- The gap in scientific knowledge
- Lack of authoritative guidelines
- Downplaying the symptoms of populations not appropriately represented in clinical trials - women, third gender, obesity, etc.
- Lack of empathy
- Absence of epistemic humility in medical professional-being humble about the fact that the knowledge of humankind requires revision in light of new evidence.
- Increase in the use of social media

**Possible Solutions**

- Respecting patient symptoms
- Accepting epistemic humility
- Investment for research
- Public awareness

objective "signs" of illness. The second group comprises patients from populations underrepresented in clinical trials—for example, female gender, patients belonging to specific races and ethnicity, third gender and patients with disability.[6-8,10]

## Why are Medical Professionals Criticized?

### The gap in scientific knowledge[8-11]

Much of the criticism voiced by the patients is attributed to the gaps in scientific knowledge of the chronic illness. Without an authoritative guideline from modern medicine, professionals may believe that the patient is suffering from factitious disorder. From a patient perspective, this compounds patient mistrust of doctors and, thus, feel gaslighted.

### Absence of epistemic humility[12]

Epistemic humility is an intellectual virtue. It means being humble about the fact that the knowledge of humankind requires revision in light of new evidence.[7] Many patients thus feel deceived when they observe doctors who lack adequate understanding of their illness. Here is the response of 2 patients suffering from long COVID illness.

"Every doctor appointment induced a lot of anger about their inability to process emerging studies which I (even though my brain fogged) explained to

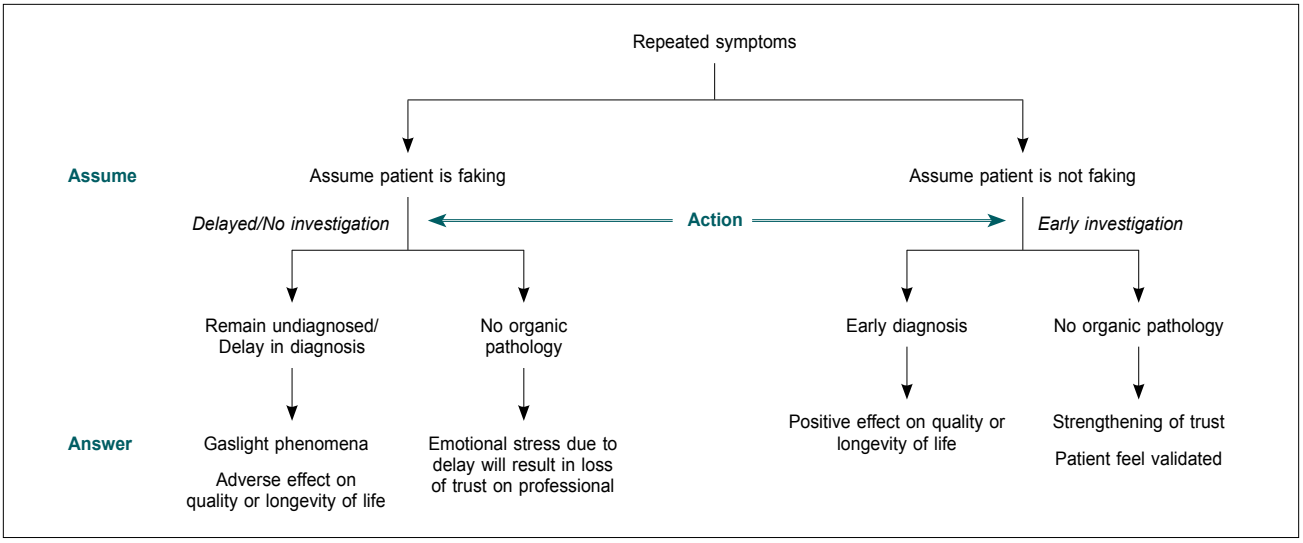


**Figure 2.** Impact of medical gaslighting.

them. They even lacked basic knowledge about human biology, immunology to understand these studies. For that reason, I stopped going to doctors."[13]

The second reference comes from COVID-19 Together, an online community[14]

Caller 1

Just call your doctor or nurse to find out.

Caller 2

The thing is that I believe that folks on the Internet know more than medical professionals nowadays. Every day we find out something new about the coronavirus. But doctors and nurses don't have any free time for reading and to keep up to date with the news now.

### Role of social media[11,14]

Amid the deep uncertainty of modern medicine in treating patients with contested illnesses, patients are using popular social media groups to share tremendous difficulty while dealing with medical professionals, the limitations of modern medicine and the role of alternative medicines.[8-11] Patients are framing these experiences as 'Medical gaslighting'. Initially, a tiny size, post-COVID-19, there was a dramatic increase in the size of online communities that shared and popularized the term Gaslighting in the medical context.

### Best Possible Solution for Such Disharmony

To establish harmony, the gesture of a medical professional must show a sense of genuine concern and the presence of epistemic humility, while treating patients with contested illnesses. From a patient's perspective, the impact of medical gaslighting varies from loss of trust in the medical community to loss of life (Fig. 2). Respecting patients' symptoms, showing deep concern, validating symptoms with the relevant investigation and offering the best available treatment, will keep the thin thread of trust between the community and medical fraternity intact and firm.

In the era of social media, regular campaigns of credible information may help to counter lay experts' knowledge. There is also a need to invest in medical research to settle uncertainties in the guidelines of many chronic illnesses.

## CONCLUSION

Medical gaslighting results from the patient's agony because of his tremendous difficulties in contending with his illness. Gaps in scientific knowledge and a missing empathy toward them makes patients feel deceived and gaslighted. Although there exist gaps in scientific knowledge, the intent to provide guideline-directed medical treatment will put patients in a better situation. A genuine concern of medical professionals while treating a patient with contested illnesses might overshadow the ghosts of medical gaslighting.

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## Frequent Daytime Napping and Risk of Type 2 Diabetes

Individuals who nap during the week for 4 hours or more and have high body fat percentage (BFP) and C-reactive protein (CRP) levels are at greater risk of incident type 2 diabetes, suggests a study published online April 13, 2023 in the *Journal of Diabetes*.[1]

To examine the link between the frequency of napping during the daytime and risk of type 2 diabetes, researchers enrolled 4,35,342 participants without diabetes from the UK Biobank. Information about the frequency of napping at baseline was obtained via a questionnaire with participants reporting it as never or rarely (<1/week), sometimes (1-3 times/week) or usually (≥4 times/week). A total of 2,49,813 (57.4%) participants reporting that they did not nap or only rarely during the day were categorized as "non-nappers"; 163/973 (37.7%) reported napping sometimes or "occasional nappers", while 21,556 (5.0%) reported that they napped often and were therefore grouped as "habitual nappers". A total of 17,592 cases of new type 2 diabetes were noted during a median follow-up period of 9.2 years. Both occasional nappers and habitual nappers were at a significantly higher risk of type 2 diabetes with odds ratio of 1.28 and 1.49, respectively. The risk was especially higher among men, participants younger than 55 years and those with obesity.

The study also aimed to explore if BFP and CRP had any effect on this association. "A one-SD increase in CRP levels (1.1 mg/L) was associated with a 40% increase in the risk of incident type 2 diabetes (95% CI: 37-42%), and a one-SD increase in BFP (8.5%) was associated with a 69% increase in the risk of incident type 2 diabetes". The authors noted "significant additive and multiplicative interaction (relative excess risk due to interaction [RERI] = 0.490) due to interaction between napping and BFP". Patients in the highest quartile of BFP were nearly 5-times more likely to develop type 2 diabetes with a hazard ratio (HR) of 4.45. A similar result was seen for CRP (RERI = 0.266). The risk of incident type 2 diabetes was increased nearly fourfold among habitual nappers in the highest quartile of CRP with HR of 3.66.

This study signifies the high risk of incident type 2 diabetes among participants who reported higher daytime napping frequency. High BFP and CRP levels further compounded this risk suggesting a role of "adiposity and inflammation" in this interrelationship. This association was independent of the traditional risk factors for type 2 diabetes. Maintaining a healthy body fat and reducing inflammation in the body by eating an anti-inflammatory diet, regular exercise, reducing stress and adequate good quality sleep is key to reducing the risk of diabetes.

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1. Zhou R, et al. The association between daytime napping and risk of type 2 diabetes is modulated by inflammation and adiposity: evidence from 435 342 UK-Biobank participants. J Diabetes. 2023 Apr 13.

# It is Important to Document All Findings and Facts of the Case


**Lesson:** *In Rakesh Kumar Vs. Union of India and Ors. OA No. 3622 of 2012 Decided On: 08.05.2015,* the Armed Forces Tribunal Chandigarh Regional Bench at Chandimandir observed: "*We find it not correct on the part of the petitioner to state that he was not examined for pharyngitis … Therefore, in our considered opinion, the contention of the petitioner that he was not examined for 'Granular Pharyngitis' falls flat on its face. On the contrary, it was solely in view of his previous history of Panic Attack, that the Medical Board opined that he needed to be evaluated further.*"

The petitioner filed an appeal before the Armed Forces Tribunal Chandigarh Regional Bench alleging incorrect diagnosis as a result of which he was discharged from Naval service without any pension. He said that he had granular pharyngitis, but he was not examined for the same and instead was wrongly diagnosed as panic disorder with agoraphobia. He appealed for review of his case by a new Medical Board and grant of disability pension stating that his disability was due to the service conditions. The Tribunal examined all records and statements and held that the contention of the petitioner that he was not examined for granular pharyngitis had no merit. And the disability was pre-existing and not due to the service conditions, a fact which had not been disclosed by the petitioner. The Tribunal dismissed the appeal.

## COURSE OF EVENTS

- **26.07.2010:** Appellant joined the Indian Navy as a Sailor after he was found fit on medical examination on recruitment. He was sent for ship training after undertaking basic training.
- **14.01.2011:** Petitioner took oath as a Sailor.
- **28.02.2011:** He developed suffered cough and cold problems with fever, medically termed as "Granular Pharyngitis", allegedly due to the stress and strain of training and humid sea climate.

  The Naval Doctor referred the Appellant to Senior Adviser in Psychiatry who diagnosed him to be a case of "Panic Disorder with Agoraphobia ICD No. F-40.01".
- **12.04.2011:** As per the opinion of the Specialist (Annexure R-4), the petitioner had manifested with marked anxiety repeatedly in nonthreatening conditions, had poor socio-occupational adjustment and inadequate response to treatment and, therefore, was recommended to be boarded out of service under category S5A5. There was no record of the petitioner having bronchial asthma.
- **11.05.2011:** The Appellant was invalided out of service.

## APPELLANT'S APPEAL

The Appellant filed an appeal before the Armed Force Tribunal.

"*(i) (a) To issue a direction to the respondents to review his case by holding a fresh Medical Board w.r.t. to the disease 'Granular Pharyngitis' and in case found fit, to reinstate him into service w.e.f. the date of his discharge i.e., 11.05.2011; or, alternatively,*

*(b) To grant disability pension to him on the basis of the said disease w.e.f. 11.05.2011 @ 50% disability in accordance with GOI, Ministry of Defence instructions dated 31.01.2001 with interest; and*

*(ii) To grant any other relief as the Tribunal may deem fit in the facts and circumstances of the case.*"

In his arguments before the Tribunal, the Counsel for the Appellant said that "*...the petitioner was wrongly diagnosed as a case of 'Panic Disorder with Agoraphobia ICD No. F-40.01' whereas, in fact, he was suffering from the disease 'Granular Pharyngitis' which was caused due to the sea climate and was aggravated by the stress and strain of Naval Service and, therefore, it would be in the interest of justice to order holding of a fresh Medical Board of the petitioner in respect of the actual disease 'Granular Pharyngitis'.*"

He also said that the Appellant had been found to be medically fit for service at the time of recruitment. And, as there was no record stating otherwise, he was entitled to receive disability pension because he had been medically invalided out prematurely in view of the law laid down by the Apex Court in Dharamvir Singh's case [*Dharamvir Singh v. Union of India & Others, Civil Appeal No. 4949 of 2013 (Arising out of SLP(C) No. 6940 of 2010*), decided on 2nd July, 2013].

## OBSERVATIONS OF THE ARMED FORCES TRIBUNAL

The Tribunal took note of the fact that the Appellant had refused to sign the proceedings of the Invaliding Medical Board and that the Board had answered negative to the two questions put to it (as below).

"*(i) Whether the disability existed before entering service?*

*(ii) In case the disability existed at the time of entry, was it possible that it could not be detected during the routine medical examination carried out at the time of the entry?*"

With regard to the first allegation of the Appellant that he had been wrongly diagnosed, the Tribunal observed that he had no symptoms of Granular Pharyngitis such as throat pain, fever, malaise, muscle aches and painful swallowing at the time of medical examination. Instead, the Appellant "*complained of giddiness, headache, breathing difficulty when subjected to physical activity and he himself did not complain of any symptoms of Granular Pharyngitis whatsoever. He only gave a history of sudden onset of severe itching in throat and unable to take breaths with choking sensation in throat immediately after taking a small quantity of rice at lunch on that day.*"

After reviewing the medical report, the Tribunal rejected the submission of the Appellant that he had not been examined for pharyngitis as the report clearly stated: "*No congestion. No ulceration/growth. Tongue/oral cavity NAD, i.e., no abnormality was detected. Physically patient is asymptomatic. Probably he had a laryngeal spasm and mild allergic reaction to food additives in the masala.*"

The Tribunal further said: "*We further feel convinced that the petitioner has not come to the Court with clean hands and as stated earlier, his harping on Granular Pharyngitis is a red herring. That is perhaps the reason that he is loath to even rely on his actual disability, i.e., agoraphobia and panic disorder which existed from before joining service and has made him unfit for retention in service.*"

"*The argument of the petitioner that the diagnosis of 'Panic Disorder with Agoraphobia' instead of 'Granular Pharyngitis' by the doctors is facetious and perhaps even an affront to the professional acumen of the Naval doctor who was a Senior Adviser in Psychiatry and not a quack or a roadside 'Neem Hakeem'.*"

"*We are of the opinion that this infinitesimal service of 14 days is considered too insignificant in cause time relationship to have caused the disability as being claimed by him.*"

Based on these observations, the Tribunal rejected the appeal of the Appellant "*for a direction to hold a fresh Medical Board and to reinstate him in service.*"

The Tribunal cited Dharamvir Singh's case, wherein the Supreme Court examined various provisions of the Pension Regulations, Entitlement Rules and General Rules of Guidance to Medical Officers in detail and summed up the legal position as below:

"*28. A conjoint reading of various provisions, reproduced above, makes it clear that:*

*(i) Disability pension to be granted to an individual who is invalidated from service on account of a disability which is attributable to or aggravated by military service in non-battle casualty and is assessed at 20% or over. The question whether a disability is attributable or aggravated by military service to be determined under 'Entitlement Rules for Casualty Pensionary Awards, 1982' of Appendix II (Regulation 173).*

*(ii) A member is to be presumed in sound physical and mental condition upon entering service if there is no note or record at the time of entrance. In the event of his*

*subsequently being discharged from service on medical grounds any deterioration in his health is to be presumed due to service. [Rule 5 r/w Rule 14(b)].*

*(iii) Onus of proof is not on the claimant (employee), the corollary is that onus of proof that the condition for non-entitlement is with the employer. A claimant has a right to derive benefit of any reasonable doubt and is entitled for pensionary benefit more liberally (Rule 9).*

*(iv) If a disease is accepted to have been as having arisen in service, it must also be established that the conditions of military service determined or contributed to the onset of the disease and that the conditions were due to the circumstances of duty in military service [Rule 14(c)].*

*(v) If no note of any disability or disease was made at the time of individual's acceptance for military service, a disease which has led to an individual's discharge or death will be deemed to have arisen in service [14(b)].*

*(vi) If medical opinion holds that the disease could not have been detected on medical examination prior to the acceptance for service and that disease will not be deemed to have arisen during service, the Medical Board is required to state the reasons [14(b)]; and*

*(vii) It is mandatory for the Medical Board to follow the guidelines laid down in Chapter II of the 'Guide to Medical (Military Pension), 2002 - Entitlement: General Principles', ..."*

"*As per the 'Entitlement Rules for Casualty Pensionary Awards, 1982' of Appendix II (Regulation 173, (vi) If medical opinion holds that the disease could not have been detected on medical examination prior to the acceptance for service and that disease will not be deemed to have arisen during service, the Medical Board is required to state the reasons and it is mandatory for the Medical Board to follow the guidelines laid down in Chapter II of the 'Guide to Medical (Military Pension), 2002 - 'Entitlement: General Principles', ...*"

"*We find from the above guidelines that the disability suffered by the petitioner falls in the category of a mental disorder, a mention of which has been made in sub-clauses (d) and (e) of Para 7 of the Guidelines, reproduced above. It overtly falls in the category of diseases which may be undetectable by physical examination on enrollment, unless adequate history is given at the time by the member…*"

The Medical Board had evaluated "*the disability 'Panic Disorder & Agoraphobia' as 40% for life under low medical category S5A5, further holding it to have been manifested with marked anxiety repeatedly in nonthreatening conditions which, otherwise, did not exist at the time of entry into service*". Also, the proceedings of the Medical Board have very clearly brought out the symptoms of Panic Disorder and Agoraphobia, which led to the Appellant invaliding out of the service.

The Tribunal noted that the invaliding disease had been present before the Appellant had joined the Naval service as was evident from the history of Panic Attack in 2007, which increased in frequency and intensity following a motorbike accident in 2008. "*Thus, it is clear that his disability existed from before his joining service. He did not disclose the same during recruitment medical examination. During examination by the Medical Board, he himself further revealed his previous history of Globus Hystericus, again a fact which he did not disclose during recruitment medical examination.*"

"*We feel that the inaccuracy or incompleteness of service record in entry in service was due to a non-disclosure of the essential facts by the member, e.g., pre-enrollment history or an injury, or disease or mental disorder, etc. It may also be that owing to latency or obscurity of the symptoms, a disability escaped detection on enrollment… we hold that the disability cannot be said to have been aggravated by the Naval service. Moreover, the disability having been discovered soon after joining of the petitioner and he having been discharged in his own interest in order to prevent deterioration even if it is considered that there may have been a temporary worsening during service, but if the treatment given before discharge was on grounds of expediency to prevent a recurrence, no lasting damage was inflicted by service and there would be no ground for admitting entitlement under Para 9 of the General Principles for entitlement of the disability pension.*"

## FINAL JUDGEMENT

The Tribunal concurred with the opinion of the Medical Board that "*the disability does not bear causal connection with the military service*". It also noted that it had not grounds to interfere with the rejection of the disability pension claim of the petitioner under the Pension Regulations for the Navy. The Tribunal dismissed the OA (original application) with no order as to costs.

## REFERENCE

1. Rakesh Kumar Vs. Union of India and Ors. Armed Forces Tribunal Chandigarh regional bench at Chandimandir. OA No. 3622 of 2012. Decided on: 08.05.2015.

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# HCFI Dr KK Aggarwal Research Fund

## Round Table Environment Expert Zoom Meeting on "Industrial Safety and Environmental Disasters: Awareness and Practices"

**April 30, 2023 (Sunday, 12 noon-1 pm)**

- World Day for Safety and Health at Work is observed annually on 28th April to promote the prevention of occupational accidents and diseases globally.
- Some important industrial accidents in recent years have been the Bhopal gas tragedy (1984), IOC oil depot fire in Jaipur (2009), Vizag gas leak (2020) and the chemical factory blast in Gujarat (2022).
- The Bhopal gas tragedy is considered among the world's worst industrial disasters. Over 50,000 people were exposed to methyl isocyanate (MIC) gas. Two thousand people died in the immediate aftermath with another 13,000 dying in the next 15 years. Around 1,20,000 people are still suffering from cancer, tuberculosis (TB), blindness (partial/complete), post-traumatic stress disorder (PTSD) and menstrual irregularities.
- The Vizag gas leak occurred at the LG Polymers chemical plant located on the outskirts of Visakhapatnam in the early morning of 7th May, 2020. The plant stored 2,000 metric tons of styrene in tanks, which were left unattended. The resulting vapor cloud spread over a radius of 3 km. Eleven people died and more than 1,000 fell sick after exposure to the gas. The styrene monomer must be stored at 20-22°C and it is believed that a computer glitch in the factor's cooling system allowed temperatures in the storage tanks to exceed safe levels, causing the styrene to vaporize.
- A blast in chemical factory in Gujarat in 2022 killed 6 people.
- A fire broke out in the IOC oil depot in Jaipur in 2009.
- Such accidents can happen anywhere including hotels where boilers are used. If there is corrosion in the pipes, then there can be a blast which can also lead to fatalities and injuries within the hotel. So, regular check-up is very important.
- There must be regular maintenance in projects where hazardous chemicals are used. At least once in 6 months, a shutdown of that particular area and complete check-up should be done to see if there is any kind of corrosion or blockages, which can lead to any kind of industrial accidents.
- Often analysis is done after the accident has occurred. This is not the correct approach. Instead, we have to take proactive action rather than acting only after it happens. Hence, maintenance is very important.
- The person in charge of the factory must be held responsible. There should be a strict law by the Government of India on this across the country.
- The workers in Delhi Jal Board or any water utility are exposed to many types of incidents.
- Many obnoxious gases are emitted from septic tanks, which can be fatal.
- There are some standing standard operating procedures (SOPs), which should be followed by the workers, managers, supervisors because the laborers do not know the SOPs. Mitigation is the best procedure to avoid such accidents. The manager should ensure that SOPs are followed at all the working places irrespective of the type of work.
- If there is a gas leak, the face should be immediately covered with a wet cloth.
- There are lessons to be learnt from the past accidents: recognize the costs of workplace accidents, recognize the benefits of implementing an effective safety and health system, describe the elements of an effective safety and health management system and identify three methods to prevent workplace hazards.
- Direct costs of workplace accidents include cost of treatment, cost of physician and hospital, cost of medications and cost of medical equipment.
- Indirect costs of workplace accidents include schedule delays, lower morale, increased absenteeism, poor customer relations and re-training.
- An effective safety and health program increases worker investment, management commitment and allows employers to better manage their resources, personnel and environment.
- The benefits include improvements in product, process and service quality; better morale; improved

recruiting and retention and more favorable image and reputation.

- The Government of India has notified the Occupational Safety, Health and Working Conditions Code in 2020. It encourages employers to create a proactive approach for finding and fixing hazards in the workplace.
- A safety and health system has several elements: management leadership, workers participation, hazard identification and assessment, hazard prevention and control, education and training and program evaluation and improvement.
- Various action points have been defined to enhance management leadership. The first of these includes communicating your commitment to safety and health program. This can be done by a written safety and health policy statement signed by the top management. The policy should be communicated to all workers, contractors, unions, suppliers, customers, etc.
- The second action item in management leadership is to define program goals and expectations. This can be accomplished by establishing realistic, attainable and measurable goals that demonstrate progress toward improving safety and health.
- The third action point in management leadership is allocation of resources by integrating safety and health into planning and budgeting. Allow time in workers schedule for participation.
- The fourth action item in leadership is expectation of performance. This requires defining and communicating responsibilities and authorities for accountability and setting an example for workers by following the same procedures.
- Action items have also been defined for participation of workers. The first action item is to encourage workers to report safety and health concerns. This requires establishing a process to report injuries and other safety and health concerns and empowering workers to temporarily to suspend work they feel is unsafe.
- The second is the encourage workers to participate in the safety program by providing positive reinforcement to those who participate and maintain an open-door policy.
- All workers should be involved in all aspects of the program.
- Giving workers access to safety and health information is the fourth action item in workers participation. For this, they need to be given information to understand safety and health hazards.
- Barriers for participation should be removed (action item 5). Workers from all levels of the organization should be able to participate regardless of their skill level, education or language. The policies and programs should not discourage worker participation.
- The action items for hazard identification include collection of existing information about workplace hazards, route inspection of the workplace (workflow, equipment, materials using checklists), conduct incident investigations immediately (root cause analysis), identify hazards associated with emergency and non-routine situation by assessing foreseeable emergency scenarios. Table top exercises should be conducted to plan and test the response plan and procedures. Another action point in hazard identification is to characterize the nature of identified hazards, determine the controls to be implemented and prioritize the hazards for control.
- Action items have been also defined for hazard prevention and control. The first is to identify control options by reviewing literature, OSHA standards, NIOSH publications and also seeking inputs from workers, safety consultants. The other action items are selection of controls (by using hierarchy of controls); developing and updating a hazard control plan; selecting controls for emergency and non-routine operations; implementing selected controls in the workplace and doing a follow-up to confirm that the controls are effective by regular inspections and tracking progress and implementation.
- Hazard prevention and control protects workers from hazards, helps avoid injuries, illnesses and incidents; minimizes or eliminates safety and health risks and helps employers to provide safe and healthy working conditions.
- Education and training are important components of a safety and health system. Action points to accomplish this are providing training for program awareness to all managers, supervisors and workers including temporary workers on safety policies and procedures. The training should be given a language and literacy level that all workers can understand. Others include training workers on specific roles and responsibilities on safety and health management system and training workers on hazard identification and controls.
- The material safety data sheets should be displayed properly.

- For program evaluation and improvement, first verify that the program is implemented and is operating, i.e., the injuries are being reported, inspections are conducted and progress in controlling hazards is tracked. Then the program deficiencies need to be corrected along with identification of opportunities to improve.
- In manufacturing industries, the safety concerns of the workers are budget based by the management. In the health hazards the lower class of labor is most affected. Temporary labors do not have any health care facility.
- A study of ASSOCHAM in 2009 states that more than 50% of IT industry professionals are not well. Many mental issues are there in service sector. In 2022, a study of World Health Organization (WHO) states that India's population is 17% to 18% of the world's population, but we have a lot of mental disease.
- Work from home also adds to mental health.
- A holistic approach is needed. It is not just a compliance issue.
- Until and unless the health of people is managed properly, we are not going to get any benefit.
- It is not only health loss, it is time loss, resource loss; it also gives a bad reputation.
- To prevent all these, it is required from top management that there is routine check-up, routine mock drills, awareness programs is followed everywhere by all including the contractual and subcontractual staff.
- A proper orientation program is essential. The worker should be given the proper training.

**Participants:** Dr Anil Kumar, Mr Vivek Kumar, Dr Dipankar Saha, Mr Pradeep Khandelwal, Mr RS Tyagi, Mr Lovekesh Chandra

## Coronavirus Updates

### India COVID-19 update: New cases drop below 10k

On May 18, 2023, India recorded 865 new cases of COVID-19, according to data from the Union Health Ministry. The active cases are now 9092. The daily positivity rate is 0.64% and the weekly positivity rate is 0.81%. Total recoveries are over 4,44 crore. The recovery rate is 98.79%. A total of 1,050 doses were administered in the last 24 hours. So far, 220.66 crore total vaccine doses have been administered in the country including 95.21 crore second dose and 22.87 crore precaution dose… (*Source: Press Information Bureau, May 19, 2023*).

### Booster doses should now include only XBB variants

A WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) has said that the new COVID-19 booster doses should include only the XBB.1 variants that are the predominant strains currently in circulation, either the XBB.1.5 or XBB.1.16 variants. The Advisory Group also recommended against including the original SARS-CoV-2 strain in the new vaccines since it is no longer in circulation… (*Source: WHO, May 18, 2023*).

### Identify red flag neurological symptoms in long COVID patients

New guidelines from the American Academy of Physical Medicine and Rehabilitation (AAPM&R) published in the journal *Physical Medicine & Rehabilitation* emphasize on identifying long COVID patients with red flag neurological symptoms such as sudden/progressive weakness or sensory changes, which could be indicative of an acute neurologic complication like stroke, Guillain-Barré syndrome or myopathy. The guidelines also suggest collaboration with physical, occupational and speech therapists so that the patient is better able to function independently… (*Source: Medscape, May 18, 2023*).

### Post-heart transplant mortality

Adults who are recipients of a heart transplant from donors with active COVID-19 infection were more likely to die at 6 months (13.8%) compared to transplants from non-COVID donors or those who had a recently resolved COVID infection (4.9%). Similar trends for mortality were observed at 1-year post-transplant; 23.2% for recipients with heart transplants from donors with active COVID versus 9.2% for recipients with heart transplants from non-COVID donors… (*Source: Medpage Today, May 17, 2023*).

### High-risk for long COVID in patients with obstructive sleep apnea

COVID-19 survivors who have obstructive sleep apnea are at 75% greater risk for developing long COVID than those who do not have sleep apnea, according to a study published in journal *Sleep*. Such patients need to be watched over carefully… (*Source: NIH, May 11, 2023*).

*With inputs from Dr Monica Vasudev*

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# India Live 2023

## EMBOLIZED MATERIAL RETRIEVAL CORONARY

**Dr Prafulla G Kerkar, Mumbai**

While traversing severely diseased coronary arteries and manipulating equipment, particularly devices with detachable components, the opportunity for loss or embolization of material in the coronary circulation presents itself. Some of the common devices embolized during percutaneous coronary intervention (PCI) are: Stents, broken balloon catheter, wire tip fragment and stuck rotablator burrs.

However, in most cases, as a result of a cracked central venous or long-term intravascular catheter, catheter fragments are frequently the commonly embolized material that needs to be removed. Although the number of incidences has come down over the past few years, owing to: Improvement in equipment design and technology, universal use of remounted stents.

Occlusion devices, stents, guidewires and pacing wires are just a few of the many embolized materials and devices that have been reported. The four main scenarios of coronary stent loss are: Partial stent loss (balloon is partially placed in the balloon); total stent loss - guidewire *in situ* and stent on the guidewire; total stent loss - with stent off the guidewire; stent loss in the aorta or peripheral circulation.

Snares are the devices used more frequently for retrieval procedures, with single-loop and multiple-loop snares being used for retrieval of most types of embolized foreign bodies. Goose neck snare is a common choice in such cases as the loop can remain coaxial to vessel lumen, can trap retrieved fragments outside the catheter, etc.

However, some of its disadvantages are: One end of the foreign body must be free and accessible; foreign body and sheath must be removed together. In this case, maintain guidewire through the sheath to maintain vascular access. Capture fragments can double up requiring larger sheath.

## GUIDE EXTENSION CATHETER – TIPS AND TRICKS

**Dr Deepak Davidson, Kottayam**

Remember to avoid accepting satisfactory backup and always prefer optimal backup.

Guide catheter extension system (GCES) represents a valuable tool for interventional cardiologists, particularly in complex cases. Guide extension catheter (GEC) increases guide backup support and is vital in complex PCI procedures.

The balloon surfing technique requires using a balloon to deliver a GEC to the "rail" and center the device away from the vessel wall and any potential vessel damage. The technique involves positioning a small balloon at the distal tip of the GEC, with half sticking out of the catheter. The balloon is used as a bumper to get past or to the lesion and minimizes the razor effect of the GEC tip. A dedicated dilator such as a Navigation catheter (Vascular Solutions, Minneapolis, MN) or a microcatheter can be utilized instead of a balloon catheter.

The balloon anchor technique involves inflating a balloon proximal to or within the target lesion to assist in GEC advancement. The balloon acts as an anchor to pull the guide extension down the vessel. It entails inflating the balloon, whether a compliant or noncompliant balloon, at the distal vessel where the lesion is located, and while the balloon is inflated, tracking the guide catheter extension system to the lesion, to the balloon.

Balloon-assisted tracking or the "inchworm" technique involves positioning an inflated balloon halfway at the distal tip of the catheter during delivery and advancing the GEC immediately as the balloon is deflated, thus advancing the GEC distally over the deflated balloon. GEC may be associated with certain complications like air embolism or dissection.

## POST-PCI STROKE

**Dr Ajit Mullasari S, Chennai**

Stroke is one of the rare complications of PCI and arguably the most feared one. Post-PCI stroke is strongly associated with higher short- and long-term mortality rates and can result in life-altering disabilities. Most post-PCI strokes are ischemic and embolic in nature. However, they are secondary to dislodgment of atherosclerotic plaque or embolization of coronary- or catheter-derived thrombus. There are two types of major stroke: Ischemic - 83% and hemorrhagic - 17%.

It has been seen that the right radial approach can theoretically increase the stroke risk due to increased wire and catheter manipulations, especially with challenging

brachiocephalic and coronary anatomy. However, a meta-analysis study showed that no statistical difference was observed in the rate of stroke between radial and femoral access. Wide adaptation of radial access in contemporary practice does not explain the increasing trend of post-PCI stroke.

When we talk about the incidence of post-PCI stroke, it occurs within 24 hours of the procedure. The overall increasing trends of the stroke can be attributed to a higher number of patients undergoing PCI in advanced age and a higher rate of cardiogenic shock. Other unique aspects of post-PCI ischemic stroke that should be acknowledged are: Thrombolysis will have a very limited effect if dislodged debris consists of atheromatous material, not thrombus. Anticoagulation during PCI increases the risk of hemorrhagic complications. The risk of access site bleeding is an obvious concern, especially in the femoral approach.

## ANCHOR BALLOON TECHNIQUE

**Dr Prathap Kumar, Kerala**

The balloon anchoring technique was initially described by Fujita in 2003 as a new technique for superior guiding catheter support during the advancement of a balloon in coronary angioplasty. Anchoring is done to increase guide catheter support. It is ideal when additional support is required to cross an occlusion with the wire. It is used:

- When there are no suitable side branches into which a balloon can be safely inflated.
- It should only be considered for crossing occlusions when there is sufficient collateral filling to guide the progression of the wire through contralateral injection. Only as a last resource when other options are not available.

A side branch anchor is used:

- When there is difficulty advancing a long, stiff stent through a tortuous vessel, especially in calcified segments.
- When a "buddy" wire does not offer sufficient support or tends to migrate proximally when the stent is advanced.

A buddy wire stent anchor is used if the proximal vessel needs stenting. A buddy wire can be inserted, and a stent deployed over the first wire. This traps the buddy wire. Trapped wire provides strong guide catheter support.

Anchor balloon techniques have several advantages, including: Keep the guiding catheter in a coaxial position. Superior backup support to cross balloon or stent. No need to exchange the guiding catheter during the procedure.

A few disadvantages associated with the anchor balloon techniques are: May injure the orifice of the coronary artery by the guiding catheter. May injure the nontarget vessel by an anchor balloon. Two balloon catheters are needed. Hence, a large lumen guiding catheter .6Fr is necessary. Damage to the balloon or dislodgment/distortion of the stent may be caused by excessive pushing of the balloon or stent delivery balloon. Overconfidence in the ability of the inflated balloon to hold the system in place may lead to stent damage or loss or even severe vessel wall damage and perforation.

## CORONARY MICROCATHETERS – WAY TO HANDLE

**Prof Ajith Pillai, Chennai**

Among the different types of microcatheters available are large-diameter microcatheters, small-diameter microcatheters, angulated microcatheters, dual-lumen microcatheters and plaque modification microcatheters.

A few characteristic features of small-diameter microcatheters are small antegrade channels, tiny septals and epicardial channels, no torque is required, and a gentle push is needed. Large-diameter microcatheters are used in antegrade wiring through a tough and calcified chronic total occlusion (CTO) along with a high penetration wire, and in retrograde septal channels when the course is straight and need a "push". Angulated microcatheters do not require a push or torque and only require dedicated angulation. Dual lumen microcatheters have parallel wiring, access side branch after wire exteriorization, and reverse wiring for the bifurcation branch at the exit for CTO.

## CTO – BASIC PRINCIPLE OR WIRE SELECTION AND HANDLING

**Dr PK Goel, Lucknow**

A wire is made up of three parts, namely proximal cap, body and distal cap. When we discuss the physics of CTO wire tracking, three factors have to be taken into consideration, i.e.,

- Wire tip force
- Resistance in loose tissue
- Resistance in plaque.

Different types of wires available include Gaia, Infiltrac and Pilot. The Gaia wire family can advance the performance of tapered wires further. Infiltrac wires reduce friction and tactile feedback arising from points

other than the wire tip and enhance wire passage through sclerotic occlusive tissue. Pilot wires employ a jacket or sleeve of polymer fitted over a conventional spring-coil core-to-tip to enhance wire shaping, torque control and steering.

However, the key relationship between these algorithms is that wire tip force should be greater than resistance in loose tissue but less than resistance in plaque. Also, it has been seen that GC backup adds to wire penetration force. But if during the wire advancement GC backs out, it indicates that the wire is too weak compared to the resistance in lesion or is heading the wrong way.

Antegrade wiring techniques or guidewire selection is based on:

- Antegrade wire escalation and lumen to lumen crossing
- Antegrade directional penetration and step down
- Parallel wire technique
- Direction re-entry in cases of inadvertent subinitial entry at distal cap
- Elective antegrade dissection and re-entry
  - CB, if proxy cap tapering
  - Knuckle wire technique, if blunt cap.
- Salvage ADR using Sting ray balloon and wire following an inadvertent subintimal entry.

Also remember, softer may not always be safer as they are not stiff enough to penetrate very hard calcium in CTO. However, they are stiff enough to penetrate the external elastic membrane and migrate into the false lumen. On one hand stiff guidewire reduces the rate deflection because of its straight directional force. But it can sometimes take wrong turn owing to the greater penetration power.

Similarly, in a softer tip guide, though it enhances the controllability within the occluded lesion, it can deflect within the lesion. Also, it has low penetration power.

While choosing the wire, the decision should be made based on these factors:

- Duration of occlusion
- Post-MI setting/none
- Micro channels+/very faint AG trickle+
- Prox cap tapered vs. blunt/flush
- Bend/Tortuosity in the CTO segment
- Calcification
- Branch point at distal cap

Wire handling principles

- Controlled Drill: 360 degree rotation with little active advancement, the wire finds its way based on wire stiffness and lesion resistance dynamics.
- Penetration: Active wire advancement with directional deflection and torque control.

Lastly to conclude, remember perseverance, patience and perfection are the qualities to heed, but the key is to "know when to stop".

## CORONARY AIR EMBOLISM

**Dr Vijay Trehan, New Delhi**

Coronary air embolism is a rare type of embolism that occurs when a bubble of air gets trapped in the blood and causes blockage in the vascular system. In most cases, coronary air embolisms are almost and always iatrogenic. The clinical presentations of the air embolism depend upon:

- Quantum of the air
- Number of the vessels affected
- Degree of stenosis
- Left ventricular function.

In some cases, a tiny air bubble injected into the unobstructed coronary of an individual with normal left ventricular ejection fraction (LVEF), especially in a high-flow state with a vasodilator, is just an angiographic phenomenon. These air bubbles might catch some attention in imaging due to adjoining contrast.

However, if a large air bubble is injected into the system, it can result in chest pain, bradycardia, atrioventricular (AV) blocks, slow flow and hypotension. Sometimes, one might have to visit multiple branches to suck the air, which is impossible with the guiding catheter.

Hence, as a key measure for reducing the possibility of an air bubble, remember, "Rapid aspiration of air out of the coronary circulation is the single most important step." Some of the other general measures are:

- Supporting the circulation by using an IV vasopressor while the coronary is getting de-aired is the quickest HD support
- Mechanical circulatory support may be needed if IV vasopressor are inadequate and resuscitation is getting prolonged.
- Other supportive drugs include IV atropine, dopamine and ADR for babies
- Temporary pacing
- Ensure anticoagulation status.

# News and Views

## Screen All Women for Breast Cancer Starting 40 Years, Says USPSTF

The United States Preventive Services Task Force (USPSTF) has suggested that all women aged 40 to 74 years should undergo screening for breast cancer biennially, i.e., once every 2 years, according to a new draft recommendation statement on May 9, 2023.[1]

Notably, the Task Force has lowered the age of initiation of screening to 40 years instead of 50 years as had been recommended in the 2016 guideline, which also said that the decision to start screening earlier than 50 years "should be an individual one".

It has been given Grade B recommendation, which according to the Task Force means that this service should be offered or provided as "*there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial*".[2]

These recommendations do not apply to high-risk women – those who have a personal history of breast cancer, presence of genetic markers (*BRCA* gene), those who have received high-dose radiation therapy to their chest when they were young or women who were found to have a high-risk lesion on earlier biopsies.

Additionally, the Task Force has made recommendations for women aged 75 years or older and women with dense breasts. It says that there is inadequate evidence if these women should undergo breast ultrasonography or magnetic resonance imaging (MRI) as screening modalities if their screening mammograms are negative. These statements have been given Grade I recommendation, which means that "*the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality or conflicting, and the balance of benefits and harms cannot be determined*".[2]

The draft recommendation statement is available on USPSTF website for comments till June 5, 2023.

### References

1. Breast cancer: screening. May 09, 2023. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/breast-cancer-screening-adults#bcei-recommendation-title-area. Accessed May 10, 2023.
2. Grade definitions. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions. Accessed May 10, 2023.

## Factors Increasing Risk of Perinatal Stroke

Smoking during pregnancy, neonatal infection and hypoglycemia are risk factors for perinatal stroke, according to a new study from New South Wales, Australia published in April 2023 issue of *The Journal of Paediatrics and Child Health*.[1]

This study analyzed 60 term infants with perinatal stroke reported between 2017 and 2019. Each infant was matched by gestational age and birth date with 3 healthy controls. There were 60% arterial strokes (neonatal arterial ischemic stroke [NAIS]), 35% venous strokes (neonatal hemorrhagic stroke [NHS] 30%, cerebral sinovenous thrombosis [CSVT] 3% and NHS + CSVT 2%) and 5% mixed strokes (NAIS + NHS 3% and NAIS + CSVT 2%). Out of the 60 cases included in the study, 57 were found to have multiple risk factors for perinatal stroke.

On univariate risk factor analysis, factors significantly associated with higher risk of perinatal stroke were low Apgar score (<7) at 1, 5 and 10 minutes of age; emergency cesarean section, abnormal cord blood gas, neonatal infection or sepsis, congenital heart disease, neonatal hypoglycemia and resuscitation at birth. While factors like multigravida, maternal age more than 35 years, history of miscarriage, stillbirth or neonatal death had lower associated risk of stroke.

On multivariate analysis, in the full multivariable logistic regression model, after adjusting for the other maternal and neonatal risk factors, the risk of perinatal stroke was markedly increased with a 1-minute Apgar score of <7 with odds ratio (OR) of 1.54. Other risk factors that were significantly associated with stroke were smoking during pregnancy with OR 1.48, 10-min Apgar score <7 (OR 1.26) and hypoglycemia (OR 1.49). In the reduced model (after selection of variables), the risk of stroke was increased by 39% with a maternal history of smoking; the risk increased 61% with a 1-min Apgar score <7, 27% with a 10-min Apgar score <7 and 39% with neonatal infection or sepsis.

Diagnosis of perinatal stroke is often challenging because of unknown cause, non-neurological presentation and multiple risk factors. This study has established exposure to smoking during pregnancy, 10-min Apgar score <7, neonatal infection and hypoglycemia as independent risk factors for perinatal stroke suggesting

a multifactorial etiology on account of prenatal, perinatal and neonatal factors.


### Reference

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## Characterization of Knee Pain in Children

Very few children with the main complaint of knee pain referred to pediatric rheumatologist are likely to be diagnosed as juvenile idiopathic arthritis (JIA), according to a study published in the March 2023 issue of *The Journal of Paediatrics and Child Health*.[1] The presence of limping and elevated laboratory markers of acute inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were strongly associated with the diagnosis of JIA.

In this single-center study, researchers retrospectively analyzed medical records of 262 children with a complaint of knee pain. These children had been referred for pediatric rheumatological evaluation between October 2012 and June 2019. They were categorized into four groups: 32 children (12.2%) had confirmed JIA, 46 (17.6%) had inflammatory knee pain other than JIA, 57 (21.7%) had non-inflammatory knee pain, while in 127 children (48.5%), no musculoskeletal disorders were diagnosed. Infection-related arthritis and Lyme arthritis were the most frequent types of arthritis in children with inflammatory pain.

Compared to the other three groups, limping was more common in children who were diagnosed with JIA (84.4%); they were also found more often to have joint swelling (65.6%), decreased range of motion of the knee joint, both passive (71.0%) and active (77.4%). More than half (54.4%) of patients with non-inflammatory pain had significantly increased pain after physical activity versus the JIA and no disorders diagnosed groups. Patients with inflammatory knee pain had significantly less difficulty in climbing stairs than those with JIA or non-inflammatory pain.

On multivariate analysis, patients with inflammatory pain had pain in multiple joints and a positive family history of autoimmune diseases (39.1% vs. ~22% in JIA vs. 14% in non-inflammatory pain). Limping was absent in patients with non-inflammatory pain; pain in joints was limited to the knee and pain increased in intensity after physical activity in this group. Limping and ESR ≥10 were the risk factors in the JIA group.

Among children in the no disorders diagnosed group, the indicators were CRP <5 mg/L, no increase in pain after physical activity and ultrasound showed no musculoskeletal abnormalities.

Children with JIA were significantly younger than those in other groups with a mean age of 5.1 years versus 13.7 in inflammatory pain, 14.4 in non-inflammatory pain and 11.8 years in children with no disorders diagnosed. The JIA group also had leukocytosis, thrombocytosis, decreased hemoglobin and hematocrit levels and increased ESR and CRP levels.

"There is a need to identify specific factors that may indicate JIA as opposed to other causes of knee pain", note the authors. This study has attempted to characterize knee pain in children and provides "clinical clues", which can help the primary care physician to decide if these children need a rheumatological consultation. Seventy percent of children with knee pain, in this study, either had non-inflammatory pain suggestive of a mechanical pathology or had an indeterminate etiology. Only little more than 10% children, who were among the youngest, had a confirmed diagnosis of JIA in this study indicating that "knee pain alone, as a chief complaint, rarely leads to a final JIA diagnosis". It highlights the significance of a "well-documented medical history and detailed clinical examination" when examining a patient with knee pain.


### Reference

1. Gorczyca D, et al. Knee pain as a reason for referral to a paediatric rheumatologist: a retrospective study. J Paediatr Child Health. 2023;59(3):439-44.


## Advantages of Continuous Glucose Monitoring in Type 1 Diabetes

Young patients with type 1 diabetes who use continuous glucose monitoring (CGM) have lower rates of severe hypoglycemia and diabetic ketoacidosis (DKA) compared to those who self-monitor their blood glucose levels suggests a study published in *The Lancet Diabetes & Endocrinology*.[1]

A total of 32,117 type 1 diabetes patients with duration of diabetes of more than 1 year were selected for this study with an objective to compare the outcomes of CGM in 10,883 patients and blood glucose monitoring in 21,234 patients. Researchers also aimed to identify factors predicting risk of acute diabetes complications in these patients. The median age of the patients was 16.8 years and they had received treatment between January 2014 and June 2021.

The rate of severe hypoglycemia was significantly lower in patients on CGM compared to those who self-monitored their blood glucose levels; 6.74 per

100 patient-years versus 8.84 per 100 patient-years with an incidence rate ratio of 0.76. The rates of DKA were also lower in the CGM group; 3.72 per 100 patient-years versus 7.29 per 100 patient-years with an incidence rate ratio of 0.51. On a similar note, patients using CGM had statistically significant lower rates of hypoglycemic coma (1.01 vs. 1.96) and severe ketoacidosis (0.44 vs. 0.93).

The rates of severe hypoglycemia were found to correlate significantly with the time below the target glucose range (70-180 mg/dL). The incidence rate ratio was 1.69 for time ranging between 4.0% to 7.9% versus <4%. For time of ≥8%, the incidence rate ratio was 2.38 compared to time <4%. Glycemic variability also influenced the rates of severe hypoglycemia.

Factors affecting risk of DKA included glycemic variability and average sensor glucose, time in target glucose range and time above the target range. The incidence rate ratio for DKA was 1.77 for mean sensor glucose ranging between 150 to 178 mg/dL versus <150 mg/dL, which jumped to 8.66 for mean sensor glucose ≥210 mg/dL versus <150 mg/dL.

These findings indicate that use of CGM can reduce the incidence of acute diabetes-related complications in children, adolescents and young adults with type 1 diabetes on insulin. CGM, more than self-monitoring of blood glucose, was better able to identify at-risk patients. These patients should be followed-up on priority with adjustment of treatment if required.

### Reference

1. Karges B, et al. Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycaemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a population-based study. Lancet Diabetes Endocrinol. 2023;11(5):314-23.

## The First FDA-approved Treatment for Agitation in Alzheimer's Disease Dementia

Brexpiprazole, the atypical antipsychotic, has been accorded US Food and Drug Administration (FDA) approval for the treatment of agitation associated with Alzheimer's disease dementia.[1] The drug is available as oral tablets and is already approved for use in schizophrenia in adults and children aged 13 years and older and major depressive disorder in adults. However, it is not approved for the treatment of patients with dementia-related psychosis.

Management of agitation in persons with Alzheimer's disease is challenging. Symptoms of agitation include restlessness, pacing back and forth and even aggression, both physical and verbal.

**Dose:** The starting dose is 0.5 mg once daily for the first week; increase to 1 mg once daily for the next week and to 2 mg once daily on day 15. The maximum daily dose is 3 mg, which can be given after a minimum of 14 days depending upon clinical response and tolerability.

**Side effects:** Headache, dizziness, urinary tract infection, nasopharyngitis and sleep disturbances (somnolence and insomnia).

**Warning:** Brexpiprazole carries a Boxed Warning about risk of increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behaviors.

### Reference

1. FDA news release. FDA approves first drug to treat agitation symptoms associated with dementia due to Alzheimer's disease. May 11, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease. Accessed May 12, 2023.

## Lung Manifestations in Psoriasis

Psoriasis is a chronic inflammatory skin disease and is now known to be a systemic disease, instead of just being a cutaneous condition as it was considered earlier. Its association with heart disease and gastrointestinal disease such as inflammatory bowel disease is now recognized. A new study published in the journal *Respiratory Medicine* conducted a study with the aim to describe the features of lung involvement in patients with psoriasis with varying severity of the skin disease.[1]

A team of researchers from Jordan, Qatar and USA recruited 59 patients with psoriasis with no history of respiratory symptoms or active lung disease. They underwent high-resolution computed tomography (HRCT) scans of the chest to screen for subclinical pulmonary manifestations and changes in the lung parenchyma.

Nearly 80% (47/59) of the study participants were found to have abnormal findings on the HRCT scan. The most frequently reported lesions in the lungs were micronodules (66.1%), followed by nonspecific interstitial changes (32.2%), including scarring, focal ground-glass opacities and pleural-parenchymal band or atelectasis. Emphysematous changes and calcified granulomas were also found. Older patients and those with long-standing psoriasis were more likely to have these lung abnormalities. However, no correlation was noted for severity of the cutaneous manifestations.

These findings illustrate a link between lung pathology and psoriasis. Hence, physicians should screen patients

with psoriasis for possible pulmonary involvement and address them accordingly, as needed. The authors have however called for "larger multicenter studies" to verify these findings.

### Reference

1. Samrah SM, et al. Subclinical high-resolution chest CT scan features in psoriasis. Respir Med. 2023;212:107226.

## A New Drug to Treat Menopausal Hot Flashes

The US FDA has approved a new drug to treat moderate to severe hot flashes associated with menopause. Fezolinetant, is a neurokinin 3 (NK3) receptor antagonist and is the first in this class of drugs.[1] The NK3 receptor is involved in the regulation of the body temperature by the brain. By binding to the receptor, fezolinetant binds to this receptor and inhibits its action.

**Contraindications:** Co-administration with CYP1A2 inhibitors (such as carbamazepine, fluvoxamine, ciprofloxacin), patients with known cirrhosis, severe renal damage or end-stage renal disease (ESRD).

**Dose:** 45 mg once daily orally; may be taken with meals or without meals. However, there is a caveat regarding administration. The drug has to be taken at the same time every day. If the dose is missed or delayed, it should be taken at the earliest. However, the same schedule should be followed the next day.

**Side effects:** Abdominal pain, diarrhea, back pain, insomnia, hot flush and raised hepatic enzymes.

**Warning and precautions:** Liver function tests should be done before starting the treatment and every 3 months for the initial 9 months of the treatment. Treatment should be discontinued if signs of liver damage such as nausea, vomiting, jaundice appear.

### Reference

1. FDA news release. FDA approves novel drug to treat moderate to severe hot flashes caused by menopause. May 12, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-drug-treatmoderate-severe-hot-flashes-caused-menopause. Accessed May 13, 2023.

## Microvascular Complications of Type 2 Diabetes and Risk of Heart Disease

To investigate the impact of microvascular diseases on the risks of macrovascular complications in patients with type 2 diabetes, Taiwanese patients with type 2 diabetes diagnosed within 1 year were identified from the National Health Insurance Research Database between January 2008 and December 2019. Patients with microvascular diseases were categorized as having diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, diabetic kidney disease and retinopathy, diabetic kidney disease and neuropathy, diabetic retinopathy and neuropathy and diabetic kidney disease, retinopathy and neuropathy.

Results published in the journal *Cardiovascular Diabetology* showed that patient who had diabetic retinopathy or diabetic kidney disease or diabetic neuropathy were at higher risk of cardiovascular disease (CVD) (such as coronary artery disease, stroke, heart failure) and related mortality versus patients who did not have a microvascular disease.

Based on propensity-score matching, three pairs of patients were defined: patients with diabetic kidney disease and retinopathy, patients with diabetic kidney disease and neuropathy and patients with diabetic retinopathy and neuropathy.

The risk of incident coronary artery disease was higher among patients with diabetic neuropathy compared to those with diabetic kidney disease with adjusted hazard ratio (aHR) of 1.07. Patients with diabetic retinopathy were more likely to suffer a stroke versus those with diabetic kidney disease with aHR of 1.11. Compared to diabetic kidney disease and diabetic retinopathy, the risk of stroke was significantly higher with diabetic neuropathy with aHR of 1.17 and 1.12, respectively. The odds of new-onset heart failure were higher with diabetic retinopathy versus diabetic kidney disease (aHR 1.43), while the risk of incident heart failure was considerably lower with diabetic neuropathy versus diabetic retinopathy (aHR 0.79).

This study has demonstrated the higher risk of CVD and related mortality in type 2 diabetes patients with early development of microvascular disease. The risk was further enhanced among those who had more than one microvascular disease. While all the three microvascular diseases investigated in this study were associated with heart disease, the risk of stroke was significant with diabetic neuropathy, while diabetic retinopathy was linked to greater risk of heart failure. "Further research may be needed to elucidate whether there are causal relationships and plausible mechanisms between retinopathy and heart failure, neuropathy and stroke" concluded the authors.

### Reference

1. Yen FS, et al. Impact of individual microvascular disease on the risks of macrovascular complications in type 2 diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol. 2023;22(1):109.

# The Vedic Meaning of Mahamrityunjaya Mantra and the Gayatri Mantra

Any activity should always engage the 3 H model of Heart, the Head, and the Hand. The same has been advocated by the western scholars of today. The concept involves that while doing any work one should ask the head for choices and then refer these choices to the heart to choose one and finally order the hands to carry out that action.

In his book 'The Seven Spiritual Laws of Success', Deepak Chopra also talks about this. He writes that conscious-based decisions are the best decisions. Before taking any decision he recommends asking the body for the signals of comfort or discomfort and if the signals of discomfort are perceived, then one should not carry out that action.

All the above concepts come from our ancient Vedic knowledge. The two main mantras of our times are the Mahamrityunjaya Mantra and the Gayatri Mantra.

The Mahamrityunjaya Mantra is from the Rig-Veda and needs initiation for attaining any Siddhi. This is the greatest reliever from all evils and reads as under:

*Om Trayambakam Yajamahe, Sugandhim Pushti Vardhanam; Urvarukmiva Bandhanaan Mrityormukshiya Maamritat.*

It means we worship Shiva – The Three-Eyed Lord; who is fragrant and nourishes all beings; May he protect us (bandhanana) from all big (urva) diseases (aarookam). May he liberate us (mokshiye) from death (mrityor), For the sake of immortality (mamritat, amrit); as the cucumber is automatically liberated, from its bondage from the creeper when it fully ripens.

The meaning of the mantra is the importance of the third eye and the benefits of its opening. The two eyes are at the level of the physical body. The third eye means the eyes of the mind and the eyes of the soul. It also indicates that in difficulty one should look inward from the eyes of the mind and ask for the choices. Like the cucumber, one should chose the good ones and drop the bad choices (*Jo acha lage use apna lo, jo bura lage use jane do*).

The mantra for the conscious-based decision comes from Gayatri Mantra:

*Om Bhur Bhuvah Suvaha; Tat-savitur Vareñyam,*
*Bhargo Devasya Dheemahi, Dhiyo Yonah Prachodayāt.*

It means we meditate on the glory of the Creator; who has created the Universe; who is worthy of Worship; who is the embodiment of Knowledge and Light; who is the remover of all Sin and Ignorance; may He enlighten our Intellect.

It talks about the importance of conscious-based decisions and its directions to the intellect to choose the right and not the convenient actions.

The Gayatri is the Vedic prayer to illuminate the intellect. Gayatri is considered as Vedasara — "the essence of the Vedas". Veda means knowledge, and this prayer fosters and sharpens the knowledge-yielding faculty. As a matter of fact, the four mahavakyas or 'core-declarations' enshrined in the four Vedas are implied in this Gayatri mantra.

Choosing the right decision from the consciousness was later defined by Buddha. He taught that before any action ask yourself the following four questions and if the answer to any of the question is no, not to indulge in that actions. These four questions are: is it the truth, is it necessary, will the actions bring happiness to you and to the others.

■■■■

**INSPIRATIONAL STORY**

# God has a Sense of Humor Too

A woman received a call that her daughter was sick. She stopped by the pharmacy to get medication, got back to her car and found that she had locked her keys inside.

She didn't know what to do, so she called home and told the baby sitter what had happened. The baby sitter told her that her daughter's fever was getting worse. She said, "You might find a coat hanger and use that to open the door." The woman looked around and found an old rusty coat hanger that had been thrown down on the ground, possibly by someone else who at some time or other had locked their keys in their car. Then she looked at the hanger and said, "I don't know how to use this."

So, she bowed her head and asked God to send her some help. Within 5 minutes an old rusty car pulled up, with a dirty, greasy, bearded man who was wearing an old biker skull rag on his head. The woman thought, "This is what you sent to help me?" But, she was desperate, so she was also very thankful.

The man got out of his car and asked her if he could help. She said, "Yes, my daughter is very sick. I stopped to get her some medication and I locked my keys in my car. I must get home to her. Please, can you use this hanger to unlock my car?"

He said, "Sure". He walked over to the car, and in less than a minute the car was opened. She hugged the man and through her tears she said, "Thank You So Much! You are a very nice man."

The man replied, "Lady, I am not a nice man. I just got out of prison today. I was in prison for car theft and have only been out for about an hour."

The woman hugged the man again and with sobbing tears cried out loud, "Oh, Thank You God! You even sent me a Professional!"

■■■■

## Migraine Sufferers at Risk of Hypertension

Persons who suffer severe headaches or migraines are 25% more likely to develop hypertension in comparison to those who do not have a history of migraine, suggests a study published in the journal *Nutrition, Metabolism & Cardiovascular Diseases*.[1] The risk was higher among women than in men.

Data from 5,716 adults from the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) was analyzed in this cross-sectional study. The research objective was to investigate the link between self-reported migraine, severe headaches and hypertension.

Out of the 5,716 participants; 1,134 (19.8%) reported migraine or severe headaches. Younger females and those with higher body mass index (BMI) were more likely to experience migraine. Those who reported migraine also had lower dietary potassium and calcium intake, lower serum total cholesterol, creatinine and hemoglobin, high estimated glomerular filtration rate (eGFR) and lower educational status compared with those without migraine. After adjusting for confounding variables, participants with migraine or severe headaches were at 25% increased risk of developing hypertension with odds ratio (OR) of 1.25.

On subgroup analyses, a positive association between migraine or severe headache and hypertension was noted in women (OR 1.39), participants with a lower BMI (≤25 kg/m$^2$) (OR 1.51) and those without diabetes (OR 1.27).

This study has demonstrated a positive correlation between migraine and hypertension. Hence, management of migraine is important to prevent onset of hypertension in this population group.

### Reference

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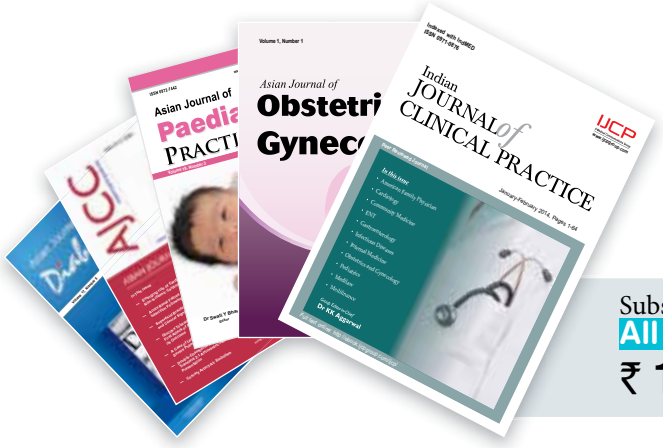

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# Lighter Side of Medicine

HUMOR

## I CHARGE YOU FOR OVERLOADING

A man driving home late at night in his Volkswagen beetle car was stopped by policemen on patrol. The police asked the man to produce his car document. When they could not fault the document, the next question to the man was: "My friend, do you realize that you committed a criminal offence by driving alone in this car at late night?"

The man became angry and responded: "How could you say that? God the father, the son and holy spirit, Prophet Elijah and Angels Micheal and Gabriel are all with me in the car."

The policeman replied: "You mean, all these people are in this small car? I charge you for overloading!"

## IF A LION IS CHASING YOU

Teacher: If a lion is chasing you, what would you do?

Student: I'd climb a tree. Teacher: if the lion climbs a tree?

Student: I will jump in the lake and swim.

Teacher: If the lion also jumps in the water and swims after you?

Student: Teacher, are you on my side or on the lion's?

## DIFFERENT PHASES OF A MAN

After engagement: Superman

After marriage: Gentleman

After 10 years: Watchman

After 20 years: Doberman

## GET ME A BATTLESHIP

After lunching at the Algonquin Hotel, Robert walked through the lobby, out the front door, and said to the uniformed man on the sidewalk, "My good man, would you please get me a taxi?"

The man immediately took offense and replied indignantly, "I'm not a doorman! I happen to be a rear admiral in the United States Navy."

Robert instantly quipped: "All right then, get me a battleship."

## ACTIVATE YOUR PHONE LINES

A young businessman had just started his own firm. He had just rented a beautiful office and had it furnished with antiques. He saw a man come into the outer office. Wishing to appear the hot shot, the businessman picked up the phone and started to pretend he had a big deal working.

He threw huge figures around and made giant commitments. Finally, he hung up and asked the visitor, "Can I help you?"

"Yeah, I've come to activate your phone lines."

## WHAT IT MEANS

Five years old Becky answered the door when the Census taker came by.

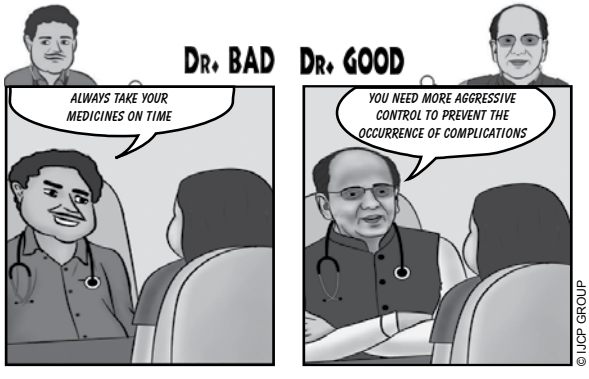
She told the Census taker that her daddy was a doctor and wasn't home, because he was performing an appendectomy.

"My," said the Census taker, "that sure is a big word for such a little girl. Do you know what it means?"

"Sure! Fifteen hundred bucks and that doesn't even include the anesthesiologist!"

## Dr. Good and Dr. Bad

**SITUATION:** A 22-year-old female with recently diagnosed T2DM presented with poor glycemic control.




**LESSON:** In comparison to the older onset T2DM, younger onset disease is associated with worse glycemic and lipid control. In addition, the prevalence of complications such as retinopathy is higher in the younger group. Thus, aggressive metabolic control is warranted in young-onset T2DM patients.

*J Diabetes Complications. 2017;31(6):971-5.*

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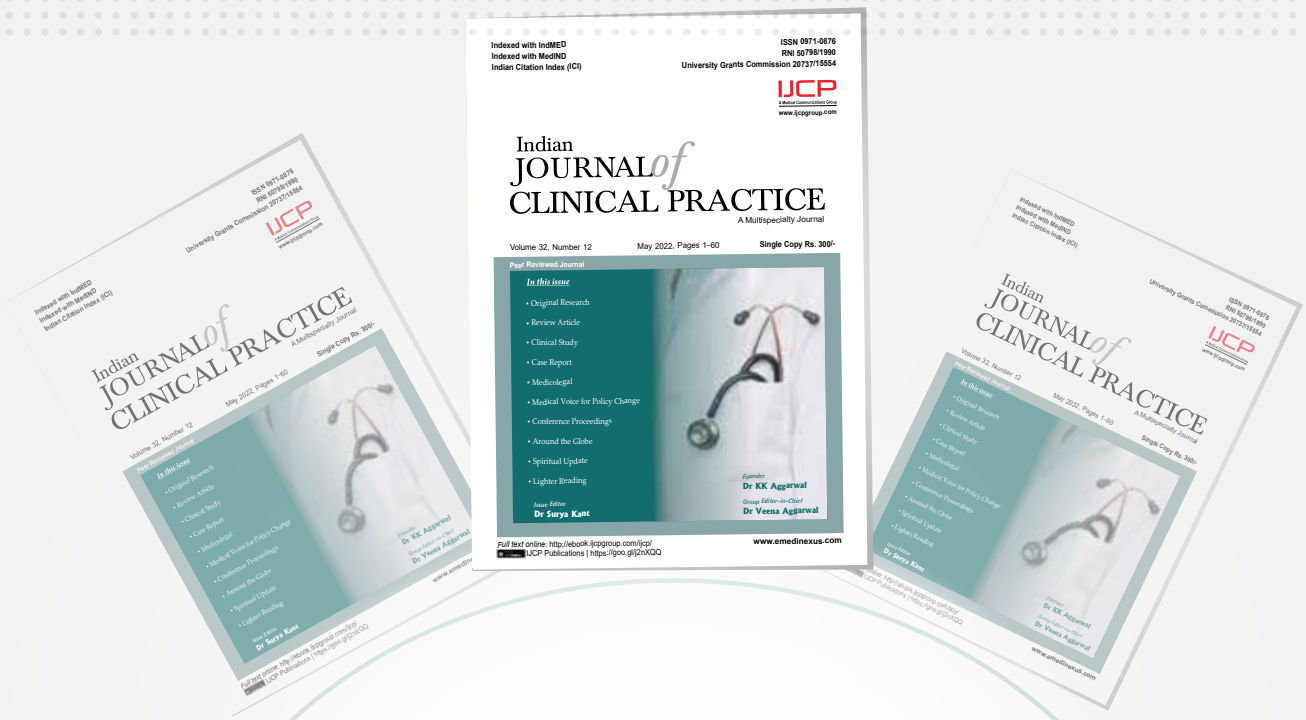


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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

### Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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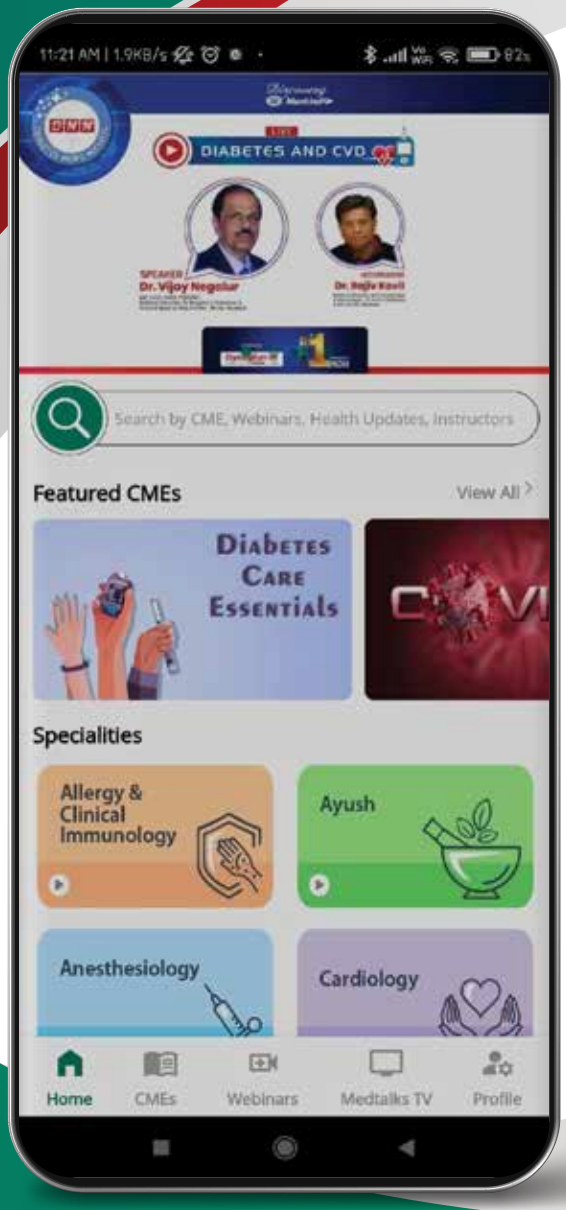


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