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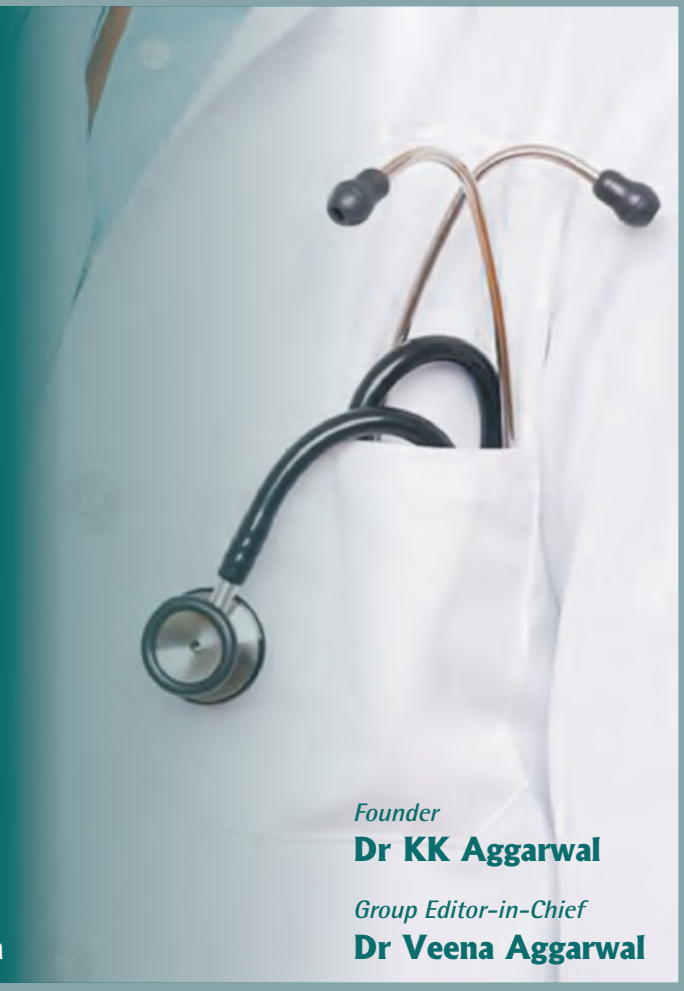

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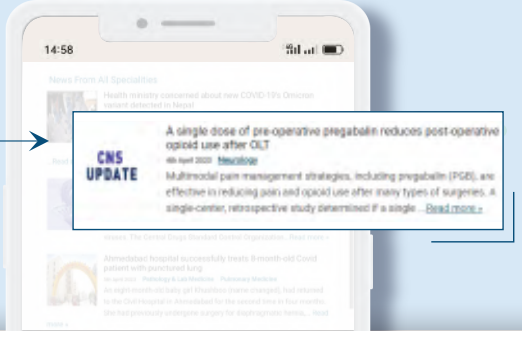

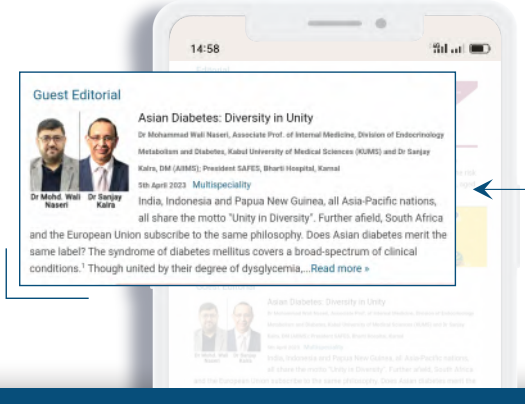

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Detecting Intra-abdominal Adhesions in Women with Repeated Cesarean Sections

Using the ultrasound sliding sign effectively differentiates between patients at high risk and low risk of intraperitoneal adhesion formation among women undergoing repeated cesarean sections, suggests a study published in the *Journal of Obstetrics and Gynaecology*[1].

The purpose of this cross-sectional study was to evaluate the efficacy of ultrasound sliding sign in predicting intraperitoneal adhesions among women undergoing repeated cesarean sections. The sliding examines the mobility of the uterus against the anterior abdominal wall using ultrasound. Women scheduled for an elective cesarean, with at least one prior cesarean delivery were eligible for the study.

To assess intraperitoneal adhesions, the sliding sign of the uterus against the anterior abdominal wall was used. A positive sliding sign was indicative of free mobility of the uterus, while a negative sliding sign indicated limited mobility. The obstetrician performing the ultrasound examination was blinded to the ultrasound results and was asked to independently report the presence or absence of adhesions during the procedure, without knowledge of the ultrasound findings.

The study involving 120 women observed that 54 patients had a negative sliding sign, while 66 patients exhibited a positive sliding sign. Subsequently, 44 out of the 54 patients with a negative sliding sign were found to have intra-abdominal adhesions during the cesarean section procedure and were categorized as the high-risk group. Conversely, no adhesions were found in any of the 66 patients with a positive sliding sign, designated as the low-risk group. The sensitivity of the sliding sign in predicting adhesions was found to be 100%, while the specificity was 86.84%. It had a positive predictive value of 81.5, a negative predictive value of 100 and had an accuracy of 91.67.

Based on the results of our study, the authors concluded that the sliding sign is an effective method for detecting intra-abdominal adhesions in women with a history of repeated cesarean delivery. The sliding sign demonstrated promising accuracy in identifying patients at risk of adhesion formation as it accurately identified all cases with confirmed adhesions and was also able to correctly identify patients without adhesions. Hence, the sliding sign is a "rapid, easy and reliable method for prediction of intraperitoneal adhesions".

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GUEST EDITORIAL

Longevity and Antiaging Medicine: Inspiration from the Past, Aspiration for the Future

SANJAY KALRA*, NAVNEET AGRAWAL†, SARITA BAJAJ‡

The science of longevity and antiaging medicine is thought to be a recent addition to the multiple specialties and subspecialties that dot the ever-expanding universe of health[1]. In reality, however, longevity and antiaging medicine is as old as humanity itself.

The first mention of efforts to attain immortality is the Samudra Manthan[2]. The Puranas, ancient Indian texts, describes the churning of the ocean as an effort by the *devas* (Gods) and *asuras* (demons) to create *amrit* (the nectar of immortality). Indian epics list seven (in some versions, eight) Chiranjeevis (immortals), whose death is not documented[3]. These include the Puranic characters - Mahabali and Parshuram, heroes from the Ramayana - Hanuman, Vibhishana, and men from the Mahabharata - Kripa, Ashwatthama, and Rishi Ved Vyasa. Some versions include Markandeya, Jambavan the bear king, Kaka Bhusundi the crow, Agastya the sage, and Narada Muni, in the list of immortals.

The Mahabharata recounts the curse of old age, placed upon Yayati, by his angry father-in-law Shukracharya, father of Devyani. Yayati exchanged his old age with his son Puru, and enjoyed a youthful life, before giving it up[4]. This episode reminds us that antiaging is feasible, even if old age is inevitable.

The Upanishads also speak of longevity, and view long life as a blessing. A similar refrain is noted in the Ayurvedic texts, *Charaka Samhita* and *Sushruta Samhita*. Both devote entire sections and multiple chapters to the study of rejuvenative, or antiaging medicine. They also treat youth-enhancing, or aphrodisiac therapy as a distinct medical subspecialty. Indian history, infact, documents the first endocrine-stimulating nutraceutical as *Chyavanprash*. It was created by the Ashwin brothers, physicians to the kings, for Rishi Chavan, who had married at an old age and required extra energy to enjoy a happy conjugal life[5].

Focus on longevity and antiaging is found in other ancient texts as well. The Sumerian Epic of Gilgamesh, considered to be the oldest book in the world, recounts the travel and travails of king Gilgamesh, as he searches for the elusive plant of immortality[6].

Modern longevity and antiaging medicine build upon this age-old inspirational aspiration. Armed with advances in biochemistry and physiology, and equipped with enhanced screening and means of monitoring health and ill health, we can proactively use newer pharmacological, nutraceutical, cosmetic, and invasive interventions to promote health and prevent disease, in a person-centered manner. This allows us to enhance the experience of aging, and to eliminate the avoidable obstacles to longevity.

Longevity and antiaging medicine is a multidisciplinary field, which works through collaboration and coordination with geriatric medicine, endocrinology and metabolism, cosmetics and dermatology as well as psychology and physical rehabilitation/physiotherapy. All specialties may be required, as per an individual's needs, to optimize outcomes[7].

As longevity and antiaging medicine develops in India, and in South Asia, we are inspired by the great minds that worked on these aspects thousands of years ago. We heed their advice on lifestyle management, on moderation in diet, on spirituality, and on environmental health. To this, we add modern monitoring and medication, used in a holistic manner, so as to improve vigor and vitality.

We do need support and sustenance from other stakeholders. Policymakers and planners must anticipate and address the growing needs of an aging population, and devise ways to utilize the productivity of this age group. Payers, such as insurance companies and government organizations, must deem pro-longevity and antiaging modalities as being worthy of reimbursement. The physician fraternity, and the paramedical profession

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should strengthen the longevity and antiaging movement by facilitating discussion and discourse around the topic. Professionals who choose this field should contribute not only in the realm of clinical care, but in academics, training, and research as well[8]. The public, too, should exercise their right to learn and understand the scope and spectrum of longevity and antiaging medicine[9].

If we work together, in a concerted and collaborative manner, with cohesion and creativity, we should be able to achieve our primary aim - optimization of health during the later years of life.

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CONSENSUS STATEMENT

The Indian Sarcopenia Staging System

SCOPE TASK FORCE

ABSTRACT

Sarcopenia is a common yet an underrecognized clinical entity that is associated with multiple health consequences including high mortality. Though diagnostic criteria are published by different international working groups, there are no unified criteria to assess severity of sarcopenia. In this brief manuscript, we propose a novel comprehensive sarcopenia staging system. This assesses risk factors, clinical presentation, and complications of sarcopenia, so as to provide a comprehensive overview of sarcopenia severity. This staging system is easy to use. It can be used not only at diagnosis but also during follow-up to assess the treatment response. However, being a novel tool, this needs validation in diverse clinical settings and across different populations.

Keywords: Sarcopenia, Indian Sarcopenia Staging System, Edmonton Obesity Staging System, Sarcopenia Severity, Sarcopenia Staging

Sarcopenia is a common syndrome that is characterized by reduced muscle strength, muscle function, and/or muscle mass[1]. Various expert groups have proposed slightly differing definitions, but the South Asian consensus defines sarcopenia in the presence of any two of the above-mentioned triad of deficits[2].

This definition, though inclusive, does not give an idea about the severity of sarcopenia. Similarly, the SARC-F questionnaire is a screening tool, and its score may not necessarily offer an accurate idea of severity. The cut-offs for tests such as hand grip strength or sit-stand test, while validated, do not provide a 360-degree assessment of sarcopenia severity[2].

NEED FOR OBJECTIVE MARKERS OF SEVERITY

It is important to determine the severity of sarcopenia, and present it in an objective manner. This allows scientific assessment of the syndrome, as well as of therapeutic interventions. An objective scoring system brings uniformity to a subjective field, encourages improvement in clinical care, and facilitates research as well. Using such a score in clinical practice facilitates risk stratification, ensures appropriate counseling and therapeutic planning, prepares one for the need for medical and supportive health care resources, as well as assists in prognosis prediction[3]. Moreover, this also helps evaluate the response to a given intervention, and facilitates crafting of tailor made therapeutic plans.

CHALLENGES

It is difficult, however, to describe the style and severity of sarcopenia in one or two words[4]. A multifactorial syndrome, sarcopenia present with complex complaints, concerns, and challenges. It is accompanied by a collection of comorbid complications and comorbidities, each of which have their own convolutions. Malnutritive, medical, surgical, orthopedic, mental, malassimilative (social) and monetary factors, all converge together in varying proportions, to form the syndrome of sarcopenia[4].

OBESITY AND SARCOPENIA

To address this situation, we take inspiration from the Edmonton Obesity Staging System (EOSS)[5]. Designed to analyze an equally perplexing disease, the EOSS stratifies obesity in five numerical stages. These stages, based upon the presence of three broad clinical complications of obesity, assessing severity of medical, mental, and functional complications[6]. This allows risk stratification and therapeutic planning in an effective and efficient manner. Moreover, this staging system has been shown to predict mortality in a much more effective manner than conventional methods of obesity assessment like body mass index.

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SARCOPENIA STAGING

On similar lines, we propose the Indian Sarcopenia Staging System (ISSS). The ISSS lists 5 stages, which are numbered from 0 to 4, based upon their severity. A descriptive term is mentioned for each stage (Table 1). These are differentiated by the presence or absence of risk factors, symptoms/signs, complications of sarcopenia, and impairment of activities of daily living (ADL). These stages can be managed by various levels of prevention (Fig. 1). Persons with mild sarcopenia may respond to dietary and exercise-based interventions, while those with moderate or severe disease will need pharmacological therapy in the form of anabolic therapy. Identification and correction of causes of secondary sarcopenia will be required at all stages[2].

- Risk factors include nonmodifiable (age, menopause, genetic syndromes) and modifiable (physical inactivity, malnutrition, chronic medical, surgical, orthopedic, or mental disease) factors.
- Signs and symptoms are best screened by SARC-F questionnaire, and confirmed by measures of muscle strength, function, and mass.
- Complications, include the medical, metabolic musculoskeletal, mood related, malassimilative (social) and monetary consequences of sarcopenia, for which causality can be demonstrated.
- Comorbidities include various medical, surgical, orthopedic, and mental conditions that are present with sarcopenia, but are not directly caused by it.

Table 1. Indian Sarcopenic Staging System

Stage		Clinical status			Level of prevention	Treatment
Numerical	Descriptive	Risk factors	Symptoms/ Signs	Complications		
0	Healthy	Absent	Absent	Absent	Primordial	Healthy lifestyle
1	Preclinical	Present	Absent	Absent	Primary	Healthy lifestyle; Treat the risk factors
2	Mild	Present	Present	Absent	Early secondary	Nutritional optimization, Exercise regimen, Treat the risk factors
3	Moderate	Present	Present	Present, without significant impairment of ADL	Advanced secondary	Nutritional optimization, Exercise regimen, Anabolic therapy, Management of complications
4	Severe	Present	Present	Present, with significant impairment of ADL	Tertiary	Nutritional optimization, Exercise regimen, Anabolic therapy, Management of complications

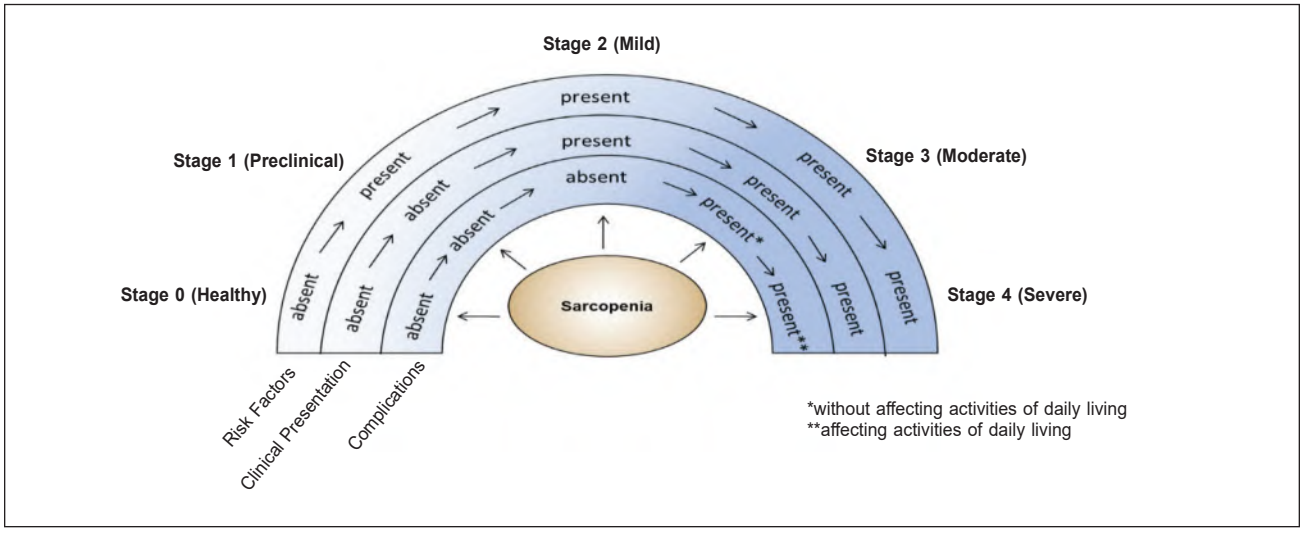

Figure 1. Indian Sarcopenic Staging System Score Card.

STRENGTHS

The ISSS lists modifiable and nonmodifiable risk factors, as well as complications and comorbidities, in a simple, reader-friendly and user-friendly style. The same scale can be used in all populations, irrespective of ethno-specific cutoffs for muscle strength.

LIMITATIONS

The ISSS needs to be used and validated in diverse clinical settings, ranging from primary care to specialist settings, and community dwellers to indoor patients. Enhanced discourse and discussion regarding the scoring system will help in improving it further as well.

THE WAY FORWARD

Sarcopenia is emerging as an important clinical and public health problem, not only in the geriatric population, but in younger age groups as well. There is a need for pragmatic and practical, staging systems to assess the severity of sarcopenia. ISSS addresses this need. Just as the EOSS has gained worldwide acceptance (202 citations as of 1 December 2024), we hope that the ISSS will be able to foster, and facilitate, better quality research in sarcopenia.

Though we use the term Indian, with pride, for the ISSS, it lends itself, humbly, to International utility and usage.

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REVIEW ARTICLE

Accuracy, Precision, Sensitivity, and Patient Preferences of Accu-Chek® Self-Monitoring Blood Glucose Meters: A Targeted Literature Review

SANJAY KALRA*, NITIN KAPOOR†, BASAVARAJ SOORAGONDA‡, RISHI SHUKLA#, SHEHLA SHEIKH¥, SRUTI CHANDRASEKARAN§, SURESH N SHINDE¶, AG UNNIKRISHNAN£, REGINA MAYOR$, CATERINA PRESENTI^, JULIA ROETSCHKE Ψ, VISHAL GALA||, ABIN AUGUSTINE||

ABSTRACT

Self-monitoring of blood glucose (SMBG) using blood glucose monitoring (BGM) devices is recommended for people with diabetes to improve glycemic control and to detect and prevent episodes of hypoglycemia in these patients. The International Organization for Standardization (ISO) and World Health Organization (WHO) have defined specific criteria for accuracy, precision, user evaluation, and interfering agents for the quality of these devices. In this targeted literature review, Accu-Chek® devices (Instant®, Guide®, Active®) were found to have stable results with appropriate accuracy and precision and did not respond to interfering agents. The devices were also found to be cost-effective and ranked high on patient preference.

Keywords: SMBG, Accu-Chek, Diabetes

Diabetes mellitus (DM) is one of the major public health concerns and one of the top non-communicable diseases. According to the 2021 International Diabetes Federation (IDF) Atlas, approximately 537 million adults are living with diabetes worldwide, with a rising prevalence in low-middle-income countries compared to high-income countries[1]. According to the Indian Council of Medical Research-India study published in 2023, the overall weighted prevalence of DM in India was reported to be 11.4%, while the prevalence of prediabetes was reported to be 15.3%[2]. The Indian Council of Medical Research (ICMR) guidelines for diabetes management recommend self-monitoring of blood glucose (SMBG) to improve glycemic control[3].

SMBG using blood glucose monitoring (BGM) devices is widely utilized worldwide to improve outcomes in DM. SMBG helps optimize treatment in both insulin-dependent and non-insulin-dependent patients. SMBG can also be used to identify hypoglycemic episodes and can help personalize therapy[4]. Further, studies have shown that frequent self-monitoring is associated with increased quality-adjusted life expectancy due to improvement in glycated hemoglobin (HbA1c) levels compared with no SMBG[5,6]. According to the World Health Organization (WHO) HEARTS D study, SMBG can be used to diagnose diabetes, albeit with a higher cut-off of 220 for post-load glucose[7].

SMBG is usually conducted with a capillary blood sample collected from a fingertip prick. However, for BGM, samples from alternate sites such as the earlobe, heel, forearm, and palm can also be utilized. BGM can also be done using venous blood, plasma, and serum. As glucose equilibrates in the aqueous portion of the sample, samples such as plasma are preferable as they have lower concentration of other blood components such as cells[8].

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Glucose meters comprise of two components including a dehydrated enzyme on the test strip and a detector. Glucose from the blood sample rehydrates the enzyme and carries out a reaction, which can be detected by the detector. Current glucometers use one of the three principle enzymatic reactions namely glucose oxidase, glucose dehydrogenase, and hexokinase[8].

Fortwaengler et al showed that inaccurate BGM is associated with additional costs when International Organization for Standardization (ISO) standards are not met[9]. More recently, continuous glucose monitoring (CGM) has been employed to help attain better glycemic control. CGM devices may improve diabetes outcomes when used in adjunct to SMBG[10].

For an SMBG device to be considered of appropriate standards, compliance with ISO 15197:2013 is the minimum requirement by the regulatory authorities. According to these recommendations, to establish system accuracy of SMBG device, ≥95% of the individual glucose measured values shall fall within ±15 mg/dL of the reference results at glucose concentrations <100 mg/dL or within ±15% at glucose concentrations ≥100 mg/dL for both the technician and the patient, and ≥99% of individual glucose measured values shall fall within Zones A and B of the Consensus Error Grid (CEG) for diabetes. Precision is defined as standard deviation (SD), which requires to be ≤3 mg/dL at glucose concentrations <100 mg/dL and the coefficient of variation (CV) shall be ≤3.0% at glucose concentrations ≥100 mg/dL. Impact of hematocrit is defined as mean bias (to reference glucose) that does not exceed ±10 mg/dL to the nominal hematocrit sample (42%) mean bias (to reference glucose) at glucose concentrations <100 mg/dL. Mean bias (to reference glucose) that does not exceed ±10% to the nominal hematocrit sample (42%) mean bias (to reference glucose) at glucose concentrations ≥100 mg/dL[11].

The WHO recommendations for intermediate precision state the criteria for repeatability (within-run variability) % CV shall be <5.0%. Usually in many countries, the % CV acceptance criterion is ≤7.1%. However, systems with higher precision (lower values of % CV) depict a product with robust quality. WHO recommends the trueness of measure to be <15% (better 10%), which means the percentage of inaccuracies obtained should be <10%[12].

Glucose dehydrogenase-glucose oxidase (GDH-GOD) based glucometers are prone to oxygen interference because oxygen is a physiological electron acceptor and is naturally affected by both low and high oxygen levels. In contrast, GDH is not affected by oxygen levels because oxygen is not involved in its electrochemical reaction[13]. WHO further recommends that all strips should have at least 12 months validity from the date of production[12]. Strips providing higher stability than 18 months are considered to be an added advantage for health care setups for cost-effective management of patients with DM. There are certain interfering agents that may confound the reading by the device, such as high hematocrit, elevated triglyceride levels, and certain drugs and environmental factors. The presence of interfering agents results in inaccurate reading by the device[14,15].

WHO has also defined criteria for the time to result. The guidelines recommend that in the case of self-monitoring/single-patient device, results should be available in less than 30 seconds (preferably <10 seconds). The devices that provide instant results in less than 5 seconds are of higher clinical significance in the decision-making process, especially in emergency cases[12]. Considering the importance of SMBG in management of DM and the standards of BGM devices, we conducted this literature review to understand how the effectiveness of a BGM device is measured in terms of achieving target glucose levels, accuracy, precision, economic analysis, and performance from published literature, especially from the point of view of those Accu-Chek® devices which are available in India (Accu-Chek® Instant®, Instant S®, Guide®, and Active®). We also sought to understand the patient and provider preferences for using these BGM devices.

METHODS

A comprehensive literature search was conducted on the PubMed databases utilizing different SMBG glucometer specific search terms. Additional searches were conducted in Google Scholar and from other review article reference lists through cross-referenced articles. The search was not limited by time, and all applicable literature was screened. Only studies conducted in human populations and published in English language were considered.

All the retrieved articles were screened for population, objectives, and use of SMBG devices. Studies reporting accuracy, precision, patient/provider preference, and economic analysis of Accu-Chek® devices (Instant®, Guide®, Active®) and only those articles with full text available in English were included.

RESULTS OF LITERATURE SEARCH

A total of 123 studies were identified. After screening for language and objectives, 93 studies were included

in the full-text screening and were further screened and assessed for the core objectives of the study: accuracy, precision, patient/provider preference, and economic analysis of the devices considered. A total of 63 studies were included in the review (Fig. 1).

ACCURACY AND PRECISION

According to the ISO standard 15197:2013, system accuracy assessment defines accuracy requirements for BGMs (ISO 15197, clause 6.3), which is calculated by performance under laboratory conditions, and user performance evaluation (ISO 15197, clause 8), which is the performance of the device under real-world scenarios[11]. According to the standards, 95% of the individual glucose results shall fall within ±15 mg/dL of the manufacturer's measurement procedure at glucose concentrations <100 mg/dL and within ±15% of glucose concentrations ≥100 mg/dL. For clinical accuracy, 99% of results should fall within Zone A + B of the CEG for type 1 diabetes. Figure 2 depicts a CEG with 100% of the test results falling within Zone A. The standard defines precision as % CV <5.0% (Table 1)[11]. In the system evaluation report for Accu-Chek® Active®, Guide®, and Instant®, which operate by the GHD-GOD mechanism, all 3 meters met all ISO requirements for accuracy and precision for multiple tested lots. The results show that the systems had 99%-100% of the data within the bias requirements, and 99%-100% of the results fell within Zone A of the CEG, clearly exceeding the acceptance criteria. The three SMBG devices were found to meet accuracy requirements in neonates and pregnant women[16-18].

In a comparative study conducted by Pleus et al, performance evaluation and system accuracy of Accu-Chek Instant® (99% and 100%) achieved ≥95% of results within ±15 mg/dL or ±15%[19].

In another study comparing 18 BGM devices conducted by Pleus et al in 126 participants, Accu-Check Guide® was found to meet the ISO 15197:2015 guidelines with 100% accuracy[20].

Further, in another study conducted by Breitenbeck et al, Accu-Chek Instant® was found to meet and exceed the ISO 15197:2013 and EN ISO 15197:2015 requirements with 100% accuracy and with all the tested lots of the BGM falling within Zone A of the CEG (Fig. 3)[21].

In a cross-sectional study, Choukem et al showed that none of the assessed glucometers met the criteria for the required level of technical accuracy of 99%; however, Accu-Chek Active® met the ISO 15197:2013 recommendations for clinical accuracy based on Parke's

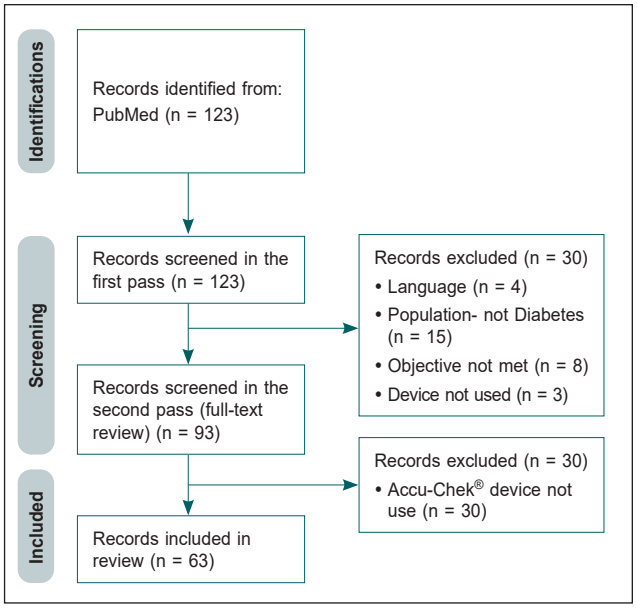

Figure 1. PRISMA flowchart.

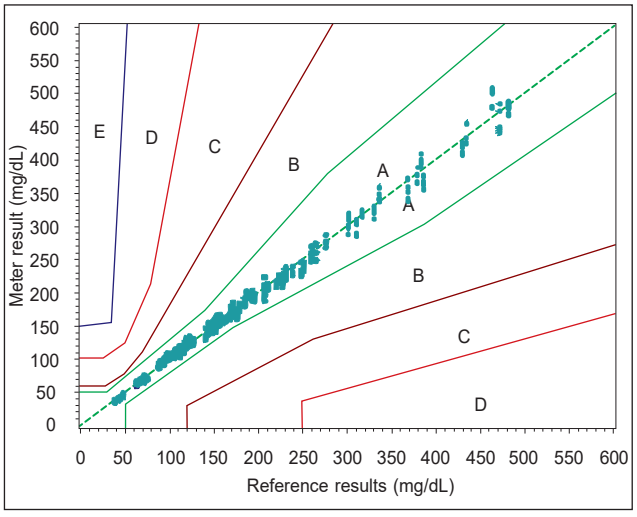

Figure 2. Consensus error grid analysis of an SMBG system showing 100% of the test results in Zone A.

CEG analysis, with 99% of values falling within Zones A and B. In this study, Accu-Chek Active® did not meet all the criteria for precision; however, it was found to be precise in the high-standard concentrations[22]. In a study conducted by Dhatt et al, Accu-Chek Active® met the criteria for the required level of accuracy of 99%, with regards to the lowest and highest proportion in the range of glycemia ≥75 mg/L (88% of results within ± 5% and 99.9% of the results within ±20%, respectively)[23]. In another study conducted by Freckmann et al comparing 4 BGM devices, including Accu-Chek Active® and Accu-Chek Performa®, showed that Accu-Chek Active® met the ISO 15197:2013 criteria for the required level of accuracy (results within ±15 mg/dL or ±15%) of 99.5%

Table 1. Acceptance Criteria for Accuracy and Precision According to ISO 15197:2013 and WHO

	ISO 15197:2013	WHO requirements
Accuracy	≥95% of the individual glucose measured values shall fall within ±15 mg/dL of the reference results at glucose concentrations <100 mg/dL or within ±15% at glucose concentrations ≥100 mg/dL. ≥99% of individual glucose measured values shall fall within Zones A and B of the CEG	Measurement range not less than from 30 to 400 mg/dL (1.7-22.2 mmol/L), preferably from 20 up to 500 mg/dL (1.1-27.8 mmol/L). Accuracy must meet ISO-15197 standard, in particular: • 95% of blood glucose results must be within 15% for values ≥100 mg/dL and 15 mg/dL for values below 100 mg/dL. • 99% of results to fall within Zones A or B of the CEG (Parke's error grid).
Precision	Standard deviation (SD) shall be ≤3.0 mg/dL at glucose concentrations <100 mg/dL. Coefficient of variation (CV) shall be ≤3.0% at glucose concentrations ≥100 mg/dL.	Repeatability (within-run variability) CV <5.0%. Must be stated in instructions for use.

against both hexokinase and glucose oxidase as reference methods in the hands of trained study personnel. The mean absolute relative difference (MARD) values (%) varied between four glucometers. Accu-Chek Active® met the ISO 15197:2003 criteria, with 100% of its values falling under Zones A and B where errors are clinically acceptable in the hands of lay users and with 100% of its values falling within ±15 mg/dL or ±20% in the hands of trained study personnel[24].

Scandinavian evaluation of laboratory equipment for primary health care (SKUP) evaluated the accuracy of Accu-Chek Instant®. The evaluation found that under optimal conditions, 100% of the results for Accu-Chek Instant® were within the allowable deviation limits for accuracy, and when handled by intended users, 99% of the results were within the limits (within ±15 mg/dL or 15%) (Fig. 3). This evaluation further indicated that Accu-Chek Instant® precision was fulfilled both under optimal conditions and by intended users compared to the glucose hexokinase method[25].

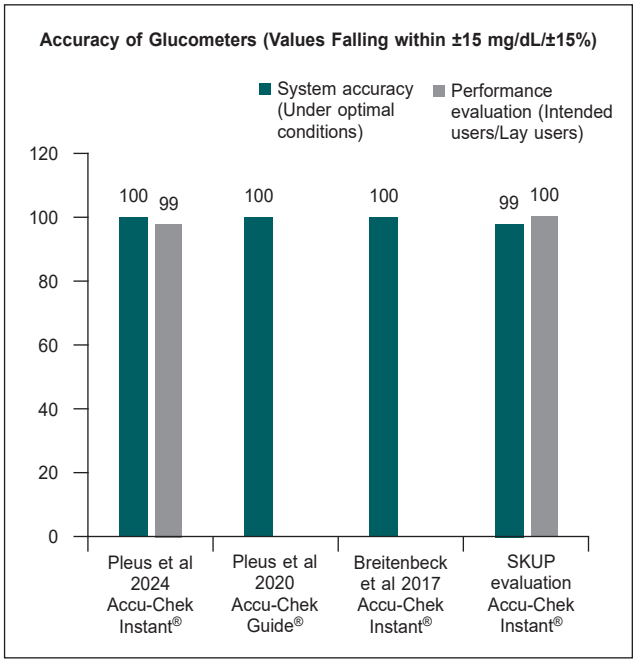

Figure 3. System accuracy and user performance for Accu-Chek Instant® and Guide®[19-21,25].

Interfering Agents

While SMBG using BGM is a fairly accurate and precise way of monitoring a patient's glucose levels, there are certain confounders or interfering agents, which can affect the outcomes of the blood test[14,15]. Table 2 summarizes the possible factors, which may interfere with test results. Interference is defined as "a cause of medically significant difference in the measured test result due to the effect of another component or property of the sample"[26]. According to ISO 15197:2013, hematocrit and interfering substances in the blood can affect the analytical performance of an SMBG system. A list showing examples of interfering substances which could be present in the blood samples is given

Table 2. Possible Reasons for Test Result Discrepancies

Error category	Error
Testing errors	• Inadequate blood sample
	• Damaged test strip
	• Improper strip storage
	• Exposure of strip to extreme heat or cold
	• Expired strip
Internal factors of patients	• Hematocrit ranges
	• Interfering substances
External factors	• Humidity
	• Inter-lab or inter-glucometer variability

in the annex of the ISO standard document. Certain examples of commonly known interfering substances include ascorbic acid, paracetamol/acetaminophen, maltose, etc. Further, for patients being treated in the intensive care unit, drugs such as cardiac inotropes and vasoconstrictors may act as interfering agents. Venous blood is the preferred sample for the evaluation of influence quantities. Hematocrit influences are required to be investigated for a minimum of five different hematocrit levels at three defined glucose concentrations. Interfering substances are required to be investigated for a minimum of two defined glucose concentrations. ISO 15197:2013 defines that influence quantities >10 mg/dL and >10% difference between the test sample and the respective control sample for glucose concentrations ≤100 mg/dL and >100 mg/dL, respectively, are required to be reported in the instructions for use along with the respective hematocrit levels or interfering substance concentrations[11].

Human factors such as incorrect use of blood glucose meters, incorrect performance of coding, inappropriate storage and usage of test strips, inappropriate education of patients and the diabetes team, manufacturing factors such as lot-to-lot variances, vial-to-vial variances, and strip-to-strip variances, and environmental factors such as temperature, humidity, altitude, and electromagnetic radiation act as external interfering agents. In addition to external factors, low hematocrit, high triglycerides, abnormal levels of bilirubin, and uric acid act as internal interfering agents[14,15]. Considering the wide variety of interfering agents, it is pertinent for a device to be unaffected by these agents and provide appropriate readings in the presence of such confounders.

According to the evaluation report of the Accu-Chek Active® system, the system had no interference from 31 tested interfering agents, except ascorbic acid, galactose, xylose, and ceftriaxone[16]. The Accu-Chek Guide® system was evaluated for interference with 202 potential interfering agents and was only found to be affected by high levels of ascorbic acid, triglycerides, and xylose[15,18]. Similar results were observed for the Accu-Chek Instant® system[17].

In various studies, topical agents such as hydroquinone-containing creams and other topical lotions and creams have been shown to be associated with significant false increase in capillary glycemia, irrespective of the enzymatic system of the glucometer used, which can lead to potentially wrong clinical decisions. Authors of these studies advocate for hand hygiene to achieve optimal responses[22,27]. Further, patients with comorbid conditions such as chronic kidney disease and hyperlipidemia have impaired blood parameters, which can potentially interfere with the accuracy of blood glucose results[14,28].

In a study conducted by Hattemer et al in patients with type 1 DM, type 2 DM, and nondiabetic population, Accu-Chek Instant® was not affected by varying hematocrit levels in the patient population[29].

Certain recent therapeutic approaches for diabetes management, such as the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors, may interfere with SMBG. However, in a study conducted by Mills et al to evaluate the effect of various SGLT2 inhibitors (Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin) on various Accu-Chek® devices (Accu-Chek Active®, Accu-Chek Aviva®, Accu-Chek Guide®, Accu-Chek Instant®, and Accu-Chek Performa®). It was concluded that canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin do not interfere with the Accu-Chek® systems at the measured concentrations[30].

SKUP evaluation concluded that glucose measurements on Accu-Chek Instant® were not affected by hematocrit within the range tested (29%-50%)[25].

User Performance Evaluation and Preference

ISO 15197:2013 requires user performance evaluation as part of accuracy assessment and is concerned with assessing whether intended users are able to obtain accurate blood glucose measurement results. According to this standard, 95% of measurements obtained within ±15 mg/dL of the reference measurement results at glucose concentrations <100 mg/dL and within ±15% at glucose concentrations ≥100 mg/dL in at least 100 people with diabetes[11]. Previously conducted research indicates that proper usage of the BGM device may positively affect patients' engagement and adherence to the treatment and may lead to an improvement in their quality of life[31,32].

In a study conducted by Pinelli et al, which investigated the patient and provider preference from 3 rounds of interviews with patients using the Accu-Chek Instant® glucometer against findings from the literature review, 89% of the participants mentioned that they would recommend the device. In this study, the majority of participants (>75%) mentioned that the backlit display made reading results easier, it was easy to apply blood on the dosing area and to eject the strip, and they could learn to operate the device without training from their health care provider[33]. In another study comparing four glucometers, including Accu-Chek Instant®, most participants agreed or completely agreed that manuals

provided with the system were clear and appropriate; this comprised instructions for use (88% agreement rate), quick reference guide (94%), and reagent system package insert (84%), with only small differences between the systems. Accu-Chek Instant® was rated to be easy to use by 99% of the participants of the study[19].

In a study conducted with 197 participants, Harvey et al found that Accu-Check Guide® meters had superior usability compared to other meters. The majority of the study participants found all aspects of the BGM system, including the test strips, strip vials, and data analysis on the BGM and the mobile app, to be acceptable for their lifestyle and to provide a better testing experience[34].

In the SKUP evaluation, user-friendliness was assessed by 88 persons with diabetes. A total of 47 participants had one or more positive comments regarding the operation facilities of Accu-Chek Instant®, and 46 participants had one or more negative comments. The meter is easy to use, has a short measuring time, needs a small amount of blood, has a convenient small size, is lightweight, easy to read the result, and has clear, large, and illuminated numbers. The large numbers were among few of the positive comments noted by the participants. The size of the strips and the convenience of handling them were noted in the negative comments[25].

Other Factors

In addition to accuracy, precision, user preference, and interfering agents, WHO and ISO standard recommendations, additional stability parameters such as storage temperature, operating temperature, altitude, humidity, etc. are also included. According to the data from system evaluation reports, Accu-Chek® Instant®, Instant S®, Guide®, and Active® significantly surpass these requirements[16-18].

Apart from the requirements of standard organizations and regulatory agencies, certain factors, such as economic analysis of the device, may be beneficial in assessing the preferability of one device over another. Economic evaluation has shown that an SMBG based on technology with software to analyze its results, accompanied by medical support, brings both health and economic benefits that can be translated into a reduced cost associated with DM[32].

When compared with newer technologies such as CGM, SMBG is an established technology and can be considered a significantly cost-effective measure, especially in markets with a predominant out-of-pocket payment by patients, such as India. The short lifetime of the CGM sensor also adds to the cost for the patient. The daily costs associated with using CGM can be as high as US$5-10, amounting to approximately US$3000 of additional costs, which is unaffordable for most of the patient population in developing countries. Also, as the technology is rapidly evolving, there can be further increases in costs related to the upgradation of the device used[10]. Additionally, though CGM may appear to be cost-effective in intensively managed patients, BGMs are considered more cost-effective in nonintensively managed patients[35,36].

Another factor contributing to the cost of CGM devices is the limited number of manufacturers developing CGM devices[37]. Though the total cost of CGM is trending downwards through the years, affordability is still an issue in developing countries. Though significant data regarding the cost-effectiveness of the two systems is still lacking, it is reasonable to conclude that SMBG and CGM can be used in a complementary manner to form an effective strategy for optimal diabetes management.

STRENGTHS AND LIMITATIONS

There are several strengths of this study. We are a group of researchers from India and have primarily focused on the Accu-Chek® devices, which are available in India. Though we found limited studies conducted in India, these data are relevant in Indian context due to the availability of the devices.

Additionally, we have not restricted ourselves to only particular type of studies. We have considered a wide range of literature including clinical studies, systematic reviews, evaluation reports released by the manufacturer and also the evaluations conducted by regulatory bodies. The inclusion of these sources makes the data robust.

However, this review is not without limitations. We have primarily focused on the devices from a single manufacturer, which precludes any comparative data. As we are a group from India, our goal is to review the existing data for various devices available in India. Comparison of variables between various devices can be an interesting topic of future research.

Further, we tried to understand the cost-effectiveness of these devices in comparison to newer technologies such as CGM, however, data was scarce and was not available for Indian scenario. This topic of understanding comparative cost-effectiveness of various devices and technologies should be assessed under comprehensive future research.

CONCLUSION

According to the widely available data, the Accu-Chek® devices (Instant®, Guide®, and Active®) are compliant with the prescribed requirements as per 15197:2013. Additionally, the devices appear to be cost-effective and are acceptable to patients based on their usability.

Acknowledgments

Ethical Declaration

As this is a noninterventional, nonhuman, and nonanimal review study, ethical approval was not required.

Data Availability

All relevant data is included in this article.

Author Contributions

SK, NK, RM, CP, JR, VG, AA had full access to the whole data set and contributed to conceptualization, data curation, formal analysis, methodology, supervision, validation, visualization, writing, review, and editing the manuscript.

BS, RS, SS, SC, SNS, AGU contributed towards methodology, validation, visualization, writing, review, and editing the manuscript.

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Conflict-of-Interest Disclosure

SK has received speaker fees from Abbott, Novo Nordisk, Roche, and Sanofi.

NK has received research grants from the National Health and Medical Research Council of Australia, Indian Council of Medical Research, and the Global Alliance for Chronic Diseases. He has also been a principal investigator for several industry-sponsored clinical trials for Novo Nordisk, Novartis, Eli Lilly, and Amgen. He is also an elected executive committee member of the governing council of the Endocrine Society of India (2022-25), All India Association for Advancing Research in Obesity (2022-25), and the Indian Society of Bone and Mineral Research (2023-2025).

BS, RS, AGU, SS, SC, and SNS declare no conflicts of interest.

RM, JR, CP, VG, and AA are employees of Roche Diabetes Care.

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RETROSPECTIVE STUDY

Effectiveness and Safety of Fixed-Dose Combination of Dapagliflozin and Linagliptin in Patients not Controlled on Glimepiride and Metformin in Real-World Settings in India: LEAD INDIA Study

D BASU*, SK PATRA†, VK BOKADIA‡, NL KAPURE#, MM MAYABHATE#, AD SHARMA#

ABSTRACT

Background: Glimepiride/metformin is commonly used in India for its cost-effectiveness and efficacy, but one-third of patients may not achieve adequate glycemic control. Dapagliflozin/linagliptin fixed-dose combination (FDC) could be an effective alternative. **Methods:** A retrospective study of type 2 diabetes patients aged >18 years, not meeting glycated hemoglobin (HbA1c) goal <7% on glimepiride and metformin. Patients received dapagliflozin (10 mg)/linagliptin (5 mg) FDC. Changes in HbA1c, fasting plasma glucose (FPG)/postprandial plasma glucose (PPG), blood pressure, and body weight were analyzed over 3 months. **Results:** The study included patient (n = 114) with a mean age of 55.15 years and mean duration of 8.5 years. Adjunct to dietary/lifestyle modifications, up-titration of metformin-glimepiride along with FDC of dapagliflozin/linagliptin demonstrated significant reduction in HbA1c (from mean 8.8 ± 1.12 to 6.92 ± 0.23; $p < 0.001$), FPG (157.8 ± 28.86 mg/dL to 113.6 ± 9.24 mg/dL; $p < 0.001$), and PPG (237.21 ± 40.58 mg/dL to 161.39 ± 12.76 mg/dL; $p < 0.001$) indicating improved glycemic control. Additionally, there was a marginal decrease in body weight (73.19 to 72.12 kg), systolic blood pressure (137.6 to 129.11 mmHg), and diastolic blood pressure (84.26 to 78.68 mmHg) largely attributed to dapagliflozin. Treatment was well-tolerated. **Conclusion:** FDC of dapagliflozin/linagliptin is an attractive therapeutic option for patients with type 2 diabetes mellitus not controlled with ongoing glimepiride and metformin.

Keywords: Type 2 diabetes mellitus, dapagliflozin, linagliptin, LEAD INDIA, glycemic control

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia stemming from insulin resistance and relative insulin deficiency. The management of T2DM typically involves a stepwise approach starting with lifestyle modifications and oral antidiabetic agents such as metformin, followed by the addition of other agents to achieve glycemic targets. Glimepiride, a sulfonylurea, and metformin, a biguanide, are commonly prescribed together due to their complementary mechanisms of action. Despite their effectiveness, a substantial proportion of patients do not attain optimal glycemic control with this combination, demanding alternative treatment strategies[1-4].

Moreover, the shortcomings of monotherapy in achieving glycemic targets can lead to increased risks of both macrovascular and microvascular complications, as well as hypoglycemic events. Therefore, combination therapies offer a more aggressive and proactive approach to managing T2DM, potentially reducing the incidence of adverse effects. Moreover, combining different drugs can reduce the pill burden on patients, which experts suggest may improve treatment adherence[1-4].

Combining sodium-glucose co-transporter 2 (SGLT2) inhibitors with dipeptidyl peptidase-4 (DPP-4) inhibitors

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in treating T2DM presents a synergistic strategy targeting multiple pathways involved in glucose regulation. SGLT2 inhibitors like dapagliflozin block renal glucose reabsorption, increasing urinary glucose excretion, and lowering plasma glucose levels independently of insulin. Meanwhile, DPP-4 inhibitors such as linagliptin enhance glucose-dependent insulin secretion and suppress glucagon release, further reducing hyperglycemia without raising the risk of hypoglycemia. This dual action addresses insulin resistance and pancreatic dysfunction, central to T2DM's pathophysiology. Clinical trials confirm that combining SGLT2 and DPP-4 inhibitors results in synergistic or additive effects on glycemic control, significantly reducing glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) levels compared to using either medication alone. Moreover, this combination therapy offers additional benefits such as weight loss, improved blood pressure, and potential cardiovascular advantages, positioning it as a promising option for comprehensive management of T2DM[5,6].

This retrospective study aimed to assess the effectiveness of dapagliflozin/linagliptin fixed-dose combination (FDC) in patients with T2DM who had failed to achieve their HbA1c goal (<7%) on a stable regimen of glimepiride and metformin. The study evaluated changes in FPG, PPG, blood pressure, body weight, and lipid profile after initiating dapagliflozin/linagliptin therapy along with safety and tolerability profile.

METHODS

Study Design and Participants

This retrospective study included adult patients with T2DM, aged >18 years, who were receiving treatment with glimepiride and metformin but had not achieved an HbA1c goal of <7%. Patients were identified from electronic medical records at a tertiary care center in India between January 2024 and April 2024. The decision to put patients to dapagliflozin/linagliptin FDC was made by treating physicians based on clinical judgment and the inability to achieve glycemic targets with the existing regimen. Out of the 190 records screened, 114 patients satisfied inclusion criteria thus were included in the study. Other all medications for respective conditions were continued as per physician's discretion.

Data Collection and Outcomes

Baseline demographic and clinical characteristics, including age, gender, duration of diabetes, and comorbid conditions, were extracted from medical records. Laboratory parameters at baseline and after 3 months of dapagliflozin/linagliptin therapy were recorded, including HbA1c, FPG, PPG, lipid profile. Blood pressure and body weight were also monitored at each visit.

Statistical Analysis

Continuous variables were expressed as mean ± SD (standard deviation) or median with interquartile range (IQR) depending on data distribution. Paired *t*-tests or Wilcoxon signed-rank tests were used to compare changes in continuous variables from baseline to 3 months post-initiation of dapagliflozin/linagliptin therapy. Categorical variables were presented as frequencies and percentages. Statistical significance was set at $p < 0.05$. All analyses were performed using statistical software (e.g., SPSS, version 20).

RESULTS

A total of 114 patients with T2DM were included in the study. The mean age of the cohort was 55.15 years, and the mean duration of diabetes was 8.5 years. The majority of patients were male (58%), mean body weight of the cohort was 73.19 kg. Significant number of patients we having comorbidities of hypertension (69.2%), dyslipidemia (54.3%), or both (36.8%) (Table 1).

At baseline, patients had suboptimal glycemic control with a mean HbA1c of 8.8% ± 1.12% even after glimepiride and metformin therapy. After 3 months of treatment with dapagliflozin/linagliptin FDC, there was a significant reduction in HbA1c to 6.92% ± 0.23% ($p < 0.001$) (Fig. 1). This corresponded to a mean reduction in HbA1c of 1.88%. Similarly, significant improvements were observed in FPG (from 157.8 ± 28.86 mg/dL to 113.6 ± 9.24 mg/dL; $p < 0.001$) and PPG (from 237.21 ± 40.58 mg/dL to 161.39 ± 12.76 mg/dL; $p < 0.001$) (Table 2).

Table 1. Baseline Characteristics

Parameters	n = 114
Males (n, %)	66 (57.8)
Females (n, %)	48 (42.2)
Age (years; mean ± SD)	55.15 ± 10.78
Body weight (kgs; mean ± SD)	73.19 ± 10.11
Duration of diabetes (years; mean ± SD)	8.47 ± 5.95
HTN (n, %)	79 (69.2)
Dyslipidemia (n, %)	62 (54.3)
Both (n, %)	42 (36.8)
Systolic BP (mmHg; mean ± SD)	137.6 ± 11.8
Diastolic BP (mmHg; mean ± SD)	84.2 ± 6.8

BP = Blood pressure; HTN = Hypertension.

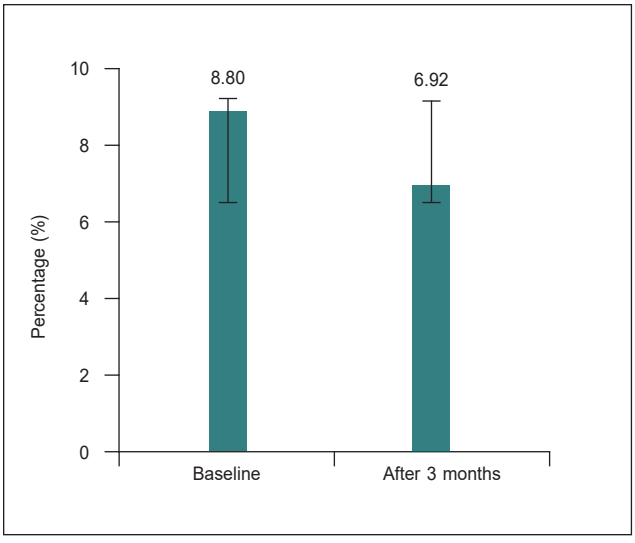

Figure 1. Change in HbA1c after 3 months of treatment with FDC of dapagliflozin + linagliptin from baseline.

Table 2. Changes in Glycemic Indices, Body Weight, Blood Pressure, and Lipid Profile from Baseline to after 3 Months of Treatment with FDC of Dapagliflozin + Linagliptin

	Parameters	Baseline	After 3 months	P value
Glycemic indices (mean ± SD)	HbA1c	8.8 ± 1.12	6.92 ± 0.23	<0.001
	FPG (mg/dL)	157.8 ± 28.86	113.6 ± 9.24	<0.001
	PPG (mg/dL)	237.21 ± 40.58	161.39 ± 12.76	<0.001
Body weight (mean ± SD)	Body weight	73.19 ± 10.11	72.12 ± 8.9	0.043
Blood pressure (mean ± SD)	Systolic (mmHg)	137.6 ± 11.8	129.1 ± 6.3	0.08
	Diastolic (mmHg)	84.2 ± 6.8	78.6 ± 4.1	0.07
Lipid profile (mean ± SD)	LDL-C (mg/dL)	123.2 ± 16.2	72.9 ± 6.8	0.023
	HDL-C (mg/dL)	32.9 ± 4.3	31.4 ± 4.1	0.067
	Triglycerides (mg/dL)	227.4 ± 31.8	150.7 ± 9.1	0.004

HbA1c = Glycated hemoglobin; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; LDL-C = Low-density lipoprotein cholesterol; HDL-C = High-density lipoprotein cholesterol.

In addition to glycemic improvements, patients experienced modest reductions in body weight (from 73.19 to 72.12 kg), systolic blood pressure (from 137.6 to 129.11 mmHg), and diastolic blood pressure (from 84.26 to 78.68 mmHg) after 3 months of dapagliflozin/linagliptin therapy. These changes were largely attributed to the SGLT2 inhibitor dapagliflozin's mechanism of action. Moreover, improvement in lipid profile was also observed, demonstrating significant reduction in low-density lipoprotein cholesterol (LDL-C) and triglycerides from baseline to after 3 months of treatment with FDC of dapagliflozin + linagliptin (Table 2).

Treatment with dapagliflozin/linagliptin FDC was generally well-tolerated, with no reports of severe hypoglycemia or significant adverse events leading to treatment discontinuation. Common side effects included mild genital mycotic infections (3%) and urinary tract infections (2%), which were managed conservatively.

DISCUSSION

The present retrospective study contributes to the growing body of evidence supporting the efficacy and safety of combining dapagliflozin and linagliptin in patients with T2DM who have inadequate glycemic control on glimepiride and metformin. The rationale behind combining SGLT2 inhibitors and DPP-4 inhibitors lies in their complementary mechanisms of action, targeting both insulin resistance, and pancreatic dysfunction.

Mechanistic Synergies

SGLT2 inhibitors, exemplified by dapagliflozin, lower blood glucose levels by inhibiting renal glucose reabsorption, leading to increased urinary glucose excretion. This mechanism operates independently of insulin secretion or action, making it effective even in patients with varying degrees of beta-cell function impairment. Conversely, DPP-4 inhibitors like linagliptin enhance endogenous insulin secretion in response to elevated blood glucose levels while suppressing glucagon secretion, thereby mitigating postprandial hyperglycemia without increasing the risk of hypoglycemia. By simultaneously targeting different pathways in glucose metabolism, the combination of dapagliflozin and linagliptin offers a comprehensive approach to improving glycemic control in T2DM[5,6].

Clinical Efficacy

Consistent with previous clinical trials and observational studies, our findings demonstrate significant improvements in glycemic parameters following initiation of dapagliflozin/linagliptin therapy. The observed reduction in HbA1c from a mean baseline of 8.8% to 6.92% after 3 months underscores the effectiveness of this combination in lowering overall

glucose levels. Furthermore, reductions in FPG and PPG levels highlight the complementary roles of SGLT2 and DPP-4 inhibition in managing both fasting and meal-induced hyperglycemia. Jain et al in phase 3 study demonstrated significant reduction in HbA1c, FPG, PPG with FDC of dapagliflozin + linagliptin in patients not controlled with metformin, findings similar to our study[7]. These results align with the concept that multifactorial interventions are pivotal in achieving and maintaining optimal glycemic targets in T2DM, particularly in patients resistant to conventional monotherapy approaches.

Additional Benefits

Beyond glycemic control, the combination of dapagliflozin and linagliptin demonstrated favorable effects on body weight and blood pressure. Modest reductions in body weight and improvements in systolic and diastolic blood pressure observed in our study are consistent with the known metabolic and cardiovascular benefits associated with SGLT2 inhibitors. These findings are of particular significance in the context of managing T2DM, where cardiovascular risk reduction remains a critical therapeutic goal[8,9].

In addition to modest reduction of body weight and blood pressure, our study has also shown improvement in lipid profile evident by reduction in LDL and triglycerides. Literature has shown promising effect on dapagliflozin on lipid metabolism, which could further contribute to its broader cardiovascular benefits in patients with T2DM. The mechanism of action of dapagliflozin involves inhibiting renal glucose reabsorption, leading to increased urinary glucose excretion and subsequent caloric loss, which in turn promotes weight reduction and improvements in insulin sensitivity. These metabolic changes are accompanied by favorable alterations in lipid profiles, as evidenced by several clinical studies[8].

Clinical trials such as the DECLARE-TIMI 58 and EMPA-REG OUTCOME trials have consistently demonstrated that treatment with SGLT2 inhibitors, including dapagliflozin, leads to reductions in circulating levels of triglycerides and LDL-C, while increasing levels of high-density lipoprotein cholesterol (HDL-C). For instance, in the DECLARE-TIMI 58 trial, dapagliflozin was associated with a significant decrease in triglyceride levels compared to placebo, with a mean change from baseline of –1.0 mmol/L ($p < 0.001$). Similarly, LDL-C levels were also reduced by –0.16 mmol/L ($p < 0.001$), and HDL-C levels increased by 0.03 mmol/L ($p < 0.001$)[9].

These lipid-modifying effects are thought to be mediated through several mechanisms. The caloric loss induced by dapagliflozin leads to increased lipolysis in adipose tissue, thereby reducing circulating triglyceride levels. Moreover, improvements in insulin sensitivity and reduction in visceral adiposity contribute to decreased hepatic synthesis of triglycerides and LDL-C. The net result is a shift towards a more favorable lipid profile, characterized by lower triglycerides, LDL-C, and higher HDL-C levels[8-10].

Safety Profile

Importantly, the safety profile of dapagliflozin/linagliptin combination therapy was favorable in our study population. Literature have shown lesser incidence of genital mycotic infection with FDC of SGLT2 inhibitor and DPP-4 inhibitors[11]. With adequate guidance on genital hygiene, our study has reported very few cases (3%) of any genital infections in our cohort. This reinforces the tolerability of combining SGLT2 and DPP-4 inhibitors, supporting their use in clinical practice for patients requiring intensified glycemic management.

Limitations and Considerations

Several limitations of our study warrant consideration. Being retrospective in nature, our study design inherently carries risks of selection bias and confounding variables that may influence outcomes. The relatively short duration of follow-up (3 months) limits our ability to assess long-term efficacy and safety outcomes associated with dapagliflozin/linagliptin therapy. Future prospective studies with larger sample sizes and longer follow-up periods are needed to further elucidate the durability of glycemic control and cardiovascular benefits associated with this combination therapy.

CONCLUSION

The findings from this retrospective study support the use of dapagliflozin/linagliptin FDC therapy as an effective and well-tolerated option for patients with T2DM inadequately controlled on glimepiride and metformin. The synergistic effects of SGLT2 and DPP-4 inhibition on glycemic control, combined with their favorable safety profile and potential cardiovascular benefits, highlight the therapeutic potential of this combination in managing T2DM comprehensively. These results underscore the importance of individualized treatment approaches tailored to address the multifaceted pathophysiology of T2DM and optimize patient outcomes.

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CLINICAL STUDY

A Controlled Clinical Study to Evaluate the Comparative Effect of Anuloma DS Tablet and Lactitol + Ispaghula Powder in Functional Constipation

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ABSTRACT

Background: The International Classification of Diseases (ICD) has described constipation as decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and/or passage of excessively hard, dry stool (ICD10-CM-K59). Overall, the average prevalence of constipation in adults has been estimated as 16% worldwide (varies between 0.7% and 79%); in adults aged 60 to 110 years, the prevalence has been estimated to be 33.5%. **Objective:** To evaluate and compare the efficacy of tablet Anuloma DS and lactitol + ispaghula powder in constipation. **Materials and methods:** Sixty-two subjects with constipation were divided into two groups: Group A with 32 subjects and Group B with 30 subjects. Group A received 1 Anuloma DS tablet at bedtime and Group B received lactitol + ispaghula powder 5 g at bedtime for 15 days. **Results:** Twenty-eight patients in Group A showed significant improvement in stool consistency, whereas just 8 patients showed improvement in consistency of stool in Group B. Twenty patients showed improvement in frequency of stool in Group A, whereas only 3 patients showed this improvement in Group B. Twenty-nine patients in Group A reported good improvement in feeling after defecation compared to 9 patients in Group B. Pain in abdomen improved in 21 patients in Group A versus 9 patients in Group B. Improvements were also seen in scores on the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. **Conclusion:** Anuloma DS showed significant clinical benefits in the treatment of constipation compared to lactitol + ispaghula powder.

Keywords: Anuloma DS, constipation, Constipation Assessment Scale, ispaghula, lactitol

The fast-paced, lifestyle adopted by many individuals in today's competitive society has had a significant impact on the health of the gastrointestinal tract resulting in a rising prevalence of gastrointestinal disorders.

Constipation, or *Vibandha*, is one such outcome. *Vibandha* is not mentioned in Ayurvedic texts as a specific disease but has been mentioned as a *Nidana* (causative factor), *Lakshana* (symptoms), and *Upadrava* (complications) of several diseases. It can be considered as a *Lakshana* in *Udavarta* (retention of feces, flatus, and urine) like *Anaha* (obstruction), *Adhmana* (distension), *Malaavastamba* (hardness of feces) due to the *Pratiloma Gati* (reverse flow) of *Apana Vayu*[1].

Vibandha (constipation) is the obstruction of the *Purisha* (feces) in the *Purishavaha Srotas* (excretory system). Constipation is a warning sign for many current or imminent disorders.

The International Classification of Diseases, (ICD10-CM-K59), defines constipation as the decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and or passage of excessively hard and dry stool. The prevalence of constipation in India is estimated to be 16.8% and that of self-reported constipation is 24.8%[2]. Overall, the average prevalence of constipation in adults has been estimated to be 16% worldwide (varies between 0.7% and 79%), whereas the prevalence in adults aged 60 to

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110 years was 33.5%[3]. Epidemiological studies show that the prevalence of constipation increases with the age and is more common in women than in men[4].

Various pharmacological agents such as bulk laxatives, stimulant laxatives, stool softeners, osmotic agents, lubricant laxatives, suppositories, and enema are used in clinical practice to treat constipation. However, their long-term use may cause electrolyte disturbance, dehydration and mineral deficiencies, and may even produce drug dependency.

Hence, there is a need for an alternative therapeutic approach, which not only manages the condition, but also minimizes the recurrence of symptoms.

Anuloma DS is an Ayurvedic proprietary medicine that contains different medicinal plants such as *Cassia lanceolata* (Senna), *Apium leptophyllum* (Ajamoda), *Cuminum cyminum* (Cumin or Jeeraka), *Terminalia chebula* (Haritaki), *Glycyrrhiza glabra* (Liquorice), *Zingiber officinale* (Ginger or Shunti), and Halite (Rock salt). These drugs are *Agnideepaka* (increase the digestive fire), *Katu Rasa* (pungent taste), *Ushna Veerya* (hot potency), and *Katu Vipaka*[5].

The primary objective of this comparative study was to evaluate the efficacy of Anuloma DS tablet and lactitol + ispaghula powder in relieving constipation. Improvements in the Quality of Life Questionnaire, Constipation Assessment Scale, and Patient Assessment Scale were the secondary objectives of the study.

METHODS

The study designed as an open-label comparative double arm clinical study enrolled 62 subjects visiting medicine OPDs of our hospital for the treatment of constipation. After screening, eligible subjects were instructed to take either Anuloma DS 1 tablet at bedtime with warm water or lactitol + ispaghula powder 5 g at bedtime with warm milk for a period of 15 days.

The inclusion criteria were male and female adults aged 18 to 70 years, who were suffering from functional constipation, were willing to sign consent form and were able to present for follow-ups.

The primary study objective assessed changes in symptoms of constipation such as consistency of stool, frequency of stool, nature of evacuation, pain in abdomen, generalized weakness, headache, body ache, and muscle cramps. Secondary end points were changes in the Constipation Assessment Scale, which evaluates 8 domains such as abdominal distension, change in amount of gas pass rectally, less frequent bowel movement, oozing of liquid stool, rectal fullness, rectal pain, small stool size, and urge but inability to pass stool. Patient assessment of constipation contain 12 domains such as discomfort- pain-bloating in abdomen, stomach cramp, painful bowel movement, rectal burning, rectal bleeding, incomplete bowel movement, hard bowel movement, small bowel movement, straining to pass bowel movement, and false alarm. And the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire is a brief but comprehensive tool, which evaluates constipation through daily individual health assessment and functioning.

Constipation was diagnosed based on the Rome IV criteria[6] as follows:

- Fewer than 3 spontaneous bowel movements per week.
- Straining for more than 25% of defecation attempts.
- Lumpy or hard stools for more than 25% defecation attempts.
- Sensation of anorectal obstruction or blockage for more than 25% of defecation attempts.
- Sensation of incomplete defecation for more than 25% of defecation attempts.
- Manual maneuvering required to defecate for more than 25% of defection attempts.

Exclusion criteria were the presence of irritable bowel syndrome, inflammatory bowel disorder, colon carcinoma, medication known to cause constipation (opioid analgesics, antidepressants, anticonvulsants, amitriptyline), uncontrolled systemic ailments or neurological illness, pregnancy and lactation.

The study participants were evaluated at baseline and two assessment points (Visit 1- Day 1 and Visit 2- Day 15). Patients underwent history and physical examination at all assessments points. They were also enquired about constipation signs and symptoms and evaluated with the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. Concomitant medication and adverse events were also assessed.

Data comparison between baseline and follow-up visit was performed using a Friedman test, Wilcoxon signed rank test, Mann-Whitney test, unpaired and paired *t*-tests. A p value of 0.05 was considered statistically significant. Statistical analysis was done using statistical software SPSS 21.0.

RESULTS

A total of 62 subjects were enrolled in the study. Two subjects were dropped as they did not come for

follow-up. Hence, 60 subjects were included in the final analysis. Age-wise distribution of subject shows that 28 subjects belong to the age group 18 to 27 years, while 10 subjects belonged to 48 to 57 years. Out of 60 subjects, 34 were females and 26 were males. Thirty-eight subjects belonged to middle class and the diet-wise distribution showed equal number in both vegetarian and mixed diet. Table 1 describes the demographic characteristics of the participants.

Assessment of Signs and Symptoms of Constipation

Constipation symptoms such as reduced appetite, distension of abdomen, pain in abdomen, general weakness, headache, body ache, muscle cramps, consistency of stool, frequency of stool, nature of evacuation, feeling after defecation were assessed on a 4-point scale. The mean symptom scores were significantly improved in Group A compared to Group B as shown in Tables 2 & 3 and Figure 1.

Constipation Assessment Scale and Patient Assessment Scale

Significant improvements were observed in the Constipation Assessment Scale and Patient Assessment Scale in Group A (Anuloma DS) ($p < 0.00$) (Table 4 and Fig. 2).

Assessment of Quality of Life

Group A had significantly greater improvement in quality of life than Group B as assessed via the Quality of Life Questionnaire (Table 5).

DISCUSSION

Constipation is a common condition that affects people of all ages. It is often erroneously attributed to the natural aging process. Although aging is associated with changes in the gastrointestinal tract and may predispose one to develop constipation, the disorder usually has a multifactorial etiology.

Etiologically, constipation can be broadly divided into two main groups: primary and secondary[7]. Primary or functional constipation is defined as constipation for more than 6 months[8], which is not due to any underlying cause such as medication side effect or an underlying medical condition. It can be distinguished from irritable bowel syndrome based on the absence of abdominal pain. It is the most prevalent type of constipation and frequently has multiple causes. Diets, such as consuming too little fiber or water, or behaviors such as engaging in less physical activity are the main culprits[9].

Table 1. Demographic Data of the Enrolled Subjects (n = 60)

Age (years)	Group A (Anuloma DS)	Group B (Lactitol + Ispaghula)
18-27	15	13
28-37	2	4
38-47	3	4
48-57	3	7
58-67	7	2
Gender	**Group A**	**Group B**
Male	13	13
Female	17	17
Diet	**Group A**	**Group B**
Mixed	15	18
Vegetarian	15	12

The incidence of gastrointestinal diseases had an unprecedented hike in recent years. This is mainly due to changes in lifestyle, food habits, behavioral changes, etc. *Annavaha Sroto dushti Vikaras* (disease of gastrointestinal system) explained in Ayurveda classics share similarity with gastrointestinal disorders in terms of etiopathogenesis and symptomatology. *Vibandha* (constipation) is a disease of *Annavaha Srotas* (gastrointestinal system) caused by disturbances of *Agni* (digestive fire). Irregular dietary habits, behavioral changes, stress, etc. lead to *Agnimandya* (weakened digestive fire), which causes *Ajeerna* (indigestion) and then constipation.

Abnormalities of *Samana* (kindling *vata*) – *Apana Vayu* (descending *vata*), *Pachaka Pitta* (digesting *pitta*), and *Kledaka Kapha* (moistening *kapha*) also play significant roles in causing constipation. Along with the difficulty in passing stools, other symptoms like pain in abdomen, flatulence, rectal pain, hemorrhoids, headache can also be associated with constipation. Chronic uncontrolled cases of constipation can lead to complications like *Udavarta*, *Vataja* gulma, *Vatodara*.

Management of constipation includes correction of *Agni*, movement of *Apana Vata* and normalizing the vitiated *Pachaka Pitta* and *Kledaka Kapha*. Different formulations like *Churna*, *Kashaya*, *Arishta*, *Ghrita* are indicated in the management of *Vibandha.*

Management of constipation in contemporary medicine includes lifestyle modifications such as introduction of high-fiber diet, plenty of water intake, physical exercise, and good bowel habits. Various classes of

Table 2. Comparison of Mean Changes in Symptom Score from V1 and V2 (n = 60)

Parameters	Group A (Study Group)			Group B (Control Group)		
	Visit	Mean score (Mean ± SD)	P value	Visit	Mean score (Mean ± SD)	P value
Reduced appetite	V1	1.40 ± 0.724	0.00	V1	1.17 ± 0.747	0.317
	V2	0.47 ± 0.507		V2	1.13 ± 0.730	
Distension of abdomen	V1	1.43 ± 0.626	0.00	V1	1.33 ± 0.711	0.01
	V2	0.40 ± 0.498		V2	1.10 ± 0.712	
Pain in abdomen	V1	0.93 ± 0.785	0.00	V1	0.70 ± 0.750	0.003
	V2	0.20 ± 0.484		V2	0.40 ± 0.498	
Generalized weakness	V1	1.03 ± 0.850	0.00	V1	0.90 ± 0.885	0.002
	V2	0.23 ± 0.430		V2	0.57 ± 0.679	
Headache	V1	0.57 ± 0.858	0.00	V1	0.50 ± 0.777	0.03
	V2	0.10 ± 0.403		V2	0.33 ± 0.606	
Body ache	V1	0.60 ± 0.770	0.00	V1	0.53 ± 0.937	0.03
	V2	0.10 ± 0.305		V2	0.37 ± 0.669	
Muscle cramps	V1	0.57 ± 0.898	0.00	V1	0.80 ± 1.031	0.01
	V2	0.17 ± 0.461		V2	0.60 ± 0.814	
Stool consistency	V1	2.27 ± 0.583	0.00	V1	2.17 ± 0.531	0.01
	V2	1.10 ± 0.305		V2	1.90 ± 0.607	
Stool frequency	V1	1.37 ± 0.556	0.00	V1	1.20 ± 0.407	0.08
	V2	1.00 ± 0.00		V2	1.10 ± 0.305	
Nature of evacuation	V1	2.33 ± 0.479	0.00	V1	2.30 ± 0.535	0.01
	V2	1.27 ± 0.450		V2	2.07 ± 0.640	
Feeling after defecation	V1	2.30 ± 0.466	0.00	V1	2.30 ± 0.596	0.01
	V2	1.20 ± 0.407		V2	2.00 ± 0.695	

Table 3. Comparison of Mean Changes in Symptom Score (n = 60)

	Reduced appetite		Distension of abdomen		Pain in abdomen		Generalized weakness		Headache	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	23.2	37.8	22.7	38.3	27.2	33.8	26.65	34.35	27.5	33.4
SR	695.0	1135.0	681.0	1149.0	816.0	1014.0	799.5	1030.0	827.0	1003.0
P	0.0		0.00		0.06		0.04		0.05	

	Body ache		Muscle cramps		Stool consistency		Stool frequency		Nature of evacuation		Feeling of defecation	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	27.8	33.1	26.3	34.7	20.3	40.7	29.0	32.0	21.1	39.9	21.3	39.3
SR	835.5	994.5	789.0	1041.0	609.0	1221.0	870.0	960.0	632.0	1198.0	639.0	1191.0
P	0.08		0.02		0.00		0.08		0.00		0.00	

MR = Mean Rank; SR = Sum Rank; P = P value.

Figure 1. Comparison of mean changes in symptom score from V1 to V2 (n = 60).

RA = Reduced appetite; DA = Distension of abdomen; PA = Pain in abdomen; GW = Generalized weakness; HD = Headache; BA = Body ache; MC: Muscle cramps; CS = Stool consistency; FS = Stool frequency; NC = Nature of evacuation; FD = Feeling after defecation.

Table 4. Comparison of Mean Changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Constipation Assessment Scale	V1	5.03 ± 2.13	0.388	<0.00	V1	5.77 ± 2.72	0.498	0.02
	V2	1.73 ± 1.20	0.225		V2	5.60 ± 2.64	0.483	
Patient Assessment Scale	V1	11.8 ± 6.08	1.110	<0.00	V1	12.3 ± 5.37	0.981	0.002
	V2	6.0 ± 3.37	0.061		V2	11.9 ± 5.10	0.931	

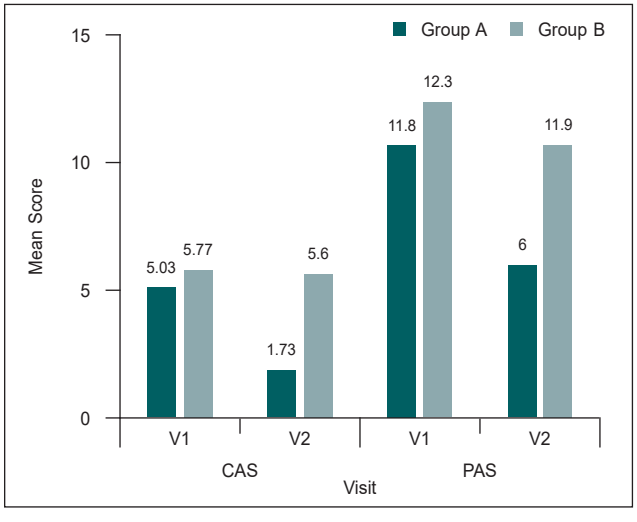

Figure 2. Comparison of mean changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60).

CAS = Constipation Assessment Scale; PAS = Patient Assessment Scale.

laxative medications include fiber supplements, osmotic laxatives, stimulant laxatives, lubricants, stool softeners, etc. Enemas and suppositories are used when the above treatments yield no result[10].

Various studies report that women are more than twice as likely to develop constipation as men. This is attributed to the slower gut transit in women due to the changing levels of progesterone and estrogen or damage to the pelvic floor in a women's obstetric history.

Considering the socioeconomical background and dietary habits of the locality, it is not possible to draw any conclusions. Out of 60 subjects, 22 were of *Vata-Kapha Prakriti* and 16 were of *Vata-Pitta Prakriti*. *Vibandha* (constipation) is a *Vata-Dosha Pradhana Vyadhi* (main disease), which may be common among people with *Vata*-predominant *Prakriti*.

In this study, patients in Group A (Anuloma DS tablet) showed significant improvement in primary and

Table 5. Comparison of Mean Changes in Quality of Life (PAC-QOL) from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Quality of life	V1	50.6 ± 13.2	2.404	<0.00	V1	49.5 ± 12.4	2.235	0.001
	V2	29.9 ± 10.3	1.886		V2	33.8 ± 11.4	2.083	

SD = Standard deviation; SE = Standard error.

secondary outcome measures compared to Group B (lactitol + ispaghula powder) after 15 days of intervention.

Appetite was improved in 26 subjects of the study group and remained same in 4 subjects. In the control group, appetite improved in 1 subject, but remained same in 29 subjects of the control group. Anuloma DS contains *Agnideepaka* herbs like *Ajamoda*, *Shunti* and *Jeeraka, Katu Rasa, Ushna Veerya*, and *Katu Vipaka*, which help in improving the appetite.

Distention of abdomen was found to be reduced in 28 subjects of study group and 7 subjects in control group after intervention. This can be attributed to the *Vata Anulomana* property of Haritaki, which properly digests the *Mala* and facilitates the passage of *Apana Vata*.

Pain in abdomen was reduced in 21 subjects and remained same in 9 subjects of study group and 9 subjects showed reduced symptoms and remained same in 21 subjects in control group. *Shunti* and *Ajamoda* possess *Shoolaghna* property, which helped reduced the abdominal pain.

Generalized weakness was reduced in 20 subjects and remained same in 10 patients. *Agnideepaka* drugs helped in normalizing the *Agni* thereby facilitating digestion and absorption. This might have helped in reducing the generalized weakness. Reduction in generalized weakness is also attributed to *Yashtimadhu*, which is a *Jeevaniya dravya* having *Balya, Glanihara*, and *Kshayahara* properties. Headache was reduced in 11 subjects, but remained the same in 19 subjects in Group A. Body ache was reduced in 13 subjects and remained same in 17 subjects. Muscle cramp was reduced in 8 subjects and remained same in 22 subjects.

Consistency of stool was improved in 28 subjects and remained same only in 2 subjects and 8 subjects improved and 22 subjects remained in control group. Haritaki is *Anulomana dravya*, which does the *Malapaka* resulting in improved consistency of stool.

Frequency of stool was improved in 20 subjects and remained same in 10 subjects and 3 subjects showed improvement and 27 subjects remain in control group. Sonamukhi is *Adhoshodhaka* (laxative) dravya and *Saindhava Lavana* is *Vibandha Hara dravya*. Both helped in improving the stool frequency.

Nature of evacuation was improved in 27 subjects and 7 subjects in study and control group, respectively. Feeling after defecation was improved in 29 subjects and 9 subjects in study group and control, respectively. This was due to the improvements observed in appetite, digestion, consistency, and frequency of stool. Ingredients of tablet Anuloma DS were not only effective in facilitating defecation, but also helped in increasing appetite and digestion. This helped in proper absorption, formation and elimination of stools. This was significantly evident in secondary outcome measures such as Constipation Assessment Scale, Patient Assessment Scale of constipation and Quality of Life Scale.

CONCLUSION

Functional constipation refers to a condition where individuals experience hard, infrequent bowel movements that are often difficult or painful to pass. It is not caused by any apparent physical abnormalities or specific diseases; instead, it is diagnosed by ruling out other potential causes.

The current study as demonstrated significant improvement in signs and symptom of constipation such as stool consistency and frequency, nature of evacuation, feeling of defecation, reduced appetite, pain and distention of abdomen, general weakness, headache, body ache, and muscle cramps with Anuloma DS tablets compared to the lactitol + ispaghula powder in patients with functional constipation. The improvement observed in PAC-QOL, Constipation Assessment Scale, Patient Assessment Scale show that Anuloma DS was highly effective for the treatment in functional constipation vis-à-vis lactitol + ispaghula powder. It was also safe as no treatment-related adverse effects were reported by any of the study participants. This beneficial effect can be attributed to the synergistic therapeutic action of its constituent herbs.

Ethics Approval

The study was undertaken after approval by the Institutional Ethics Committee.

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This corrects the article "A Controlled Clinical Study to Evaluate the Comparative Effect of Anuloma DS Tablet and Lactitol + Ispaghula Powder in Functional Constipation" published in the Indian Journal of Clinical Practice Vol. 35, No. 7, December 2024.

Vonoprazan – A Potassium-Competitive Acid Blocker: An Overview

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ABSTRACT

Vonoprazan helps in management and treatment of heartburn, peptic ulcers and gastroesophageal reflux disease. The structure, mechanism of action, and clinical applications have been discussed in this article. A brief review of literature is carried out.

Keywords: Acid peptic disorders, gastroesophageal reflux disease, peptic ulcer

Acid peptic disorders stem from unique yet interrelated pathogenic mechanisms, characterized by either heightened acid secretion or compromised mucosal defense. The diagnosis of gastroesophageal reflux disease (GERD), peptic ulcer disease and acid peptic disorders is further complicated by frequent overlap with conditions such as functional dyspepsia and irritable bowel syndrome posing challenges in clinical identification[1]. GERD is expected to remain a common cause for primary care consultations[2].

The incidence of GERD is 15.6 (range 11.046-20.714). The risk factors are age, body mass index (BMI), nonvegetarian diet, tea and coffee, tobacco, and alcohol consumption[3]. Chavan and Bhaktavatsalam found the prevalence of acid peptic disease to be very high, i.e., 38.1% in Indians[4]. Clinically, acid peptic disorders present as heartburn and regurgitation in GERD patients. They also experience extraesophageal symptoms with reflux cough syndrome, which is the most common symptom. Other symptoms include lower abdominal pain and constipation[1].

The impact of acid peptic disorders affects quality of life and causes work absenteeism and if left untreated, it may lead to complications like peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma. However, the frequency, severity, and complications of GERD depend on geographic and ethnic factors. Dietary factors are responsible to lower the frequency and severity of GERD and Barrett's esophagus[3].

POTASSIUM-COMPETITIVE ACID BLOCKERS

A novel treatment in acid-related diseases are potassium-competitive acid blockers, which include fexuprazan, revaprazan, tegoprazan, and vonoprazan. Among these, vonoprazan has undergone extensive study and was initially approved in Japan in 2015 for various acid-related diseases including gastric ulcer, duodenal ulcer, reflux esophagitis, and prevention of recurrence of ulcers as well as adjunct therapy for *Helicobacter pylori* eradication[5]. The US Food and Drug Administration (FDA) approved two vonoprazan-containing regimens for *H. pylori* treatment and also accepted a new drug application for vonoprazan for the treatment of erosive esophagitis[5]. Potassium-competitive acid blockers act at the final step in the acid secretory pathway by inhibiting the hydrogen potassium ATPase (H^+/K^+-ATPase) transporter on the luminal membrane of gastric parietal cells, the same proton pump targeted by proton pump inhibitors (PPIs). After systemic absorption, potassium-competitive acid blockers concentrate in parietal cell canaliculi and ionically bind to H^+/K^+-ATPase transporters to prevent acidifying proton secretion. Once bound, the potassium-competitive acid blockers block K^+ ion access to the proton pump. Unlike PPIs, potassium-competitive acid blockers are acid stable and thus do not require enteric coating or optimal dosing administration 30 minutes prior to meals. Additionally, they are not prodrugs and act immediately at the

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proton pump. These mechanistic differences facilitate more rapid attainment of peak plasma levels and onset of action[5].

Patients in whom lifestyle modifications are ineffective in controlling GERD symptoms can benefit from pharmacologic therapy. Acid suppression forms the cornerstone of pharmacological management for GERD. Therapeutic agents include PPIs, histamine 2 receptor antagonists, and antacids. Additionally, medications affecting gastrointestinal motility such as prokinetics are also utilized in treatment of GERD[6].

The alternative formulations of PPIs include immediate-release omeprazole and modified-release dexlansoprazole in certain regions. Dexlansoprazole MR achieves a higher percentage of time with intragastric pH >4 compared to lansoprazole. However, these formulations offer only modest advantages in acid secretion control compared to conventional PPIs[7].

There is growing interest in potassium-competitive acid blockers as promising alternatives, poised to overcome some limitations associated with PPIs[5,7]. When protons are transported by H^+,K^+-ATPase from cytoplasm to the canalicular space across the apical membrane of parietal cells, an equal amount of K^+ ions are counter transported into cytoplasm of parietal cells, so that total process is electrically balanced.

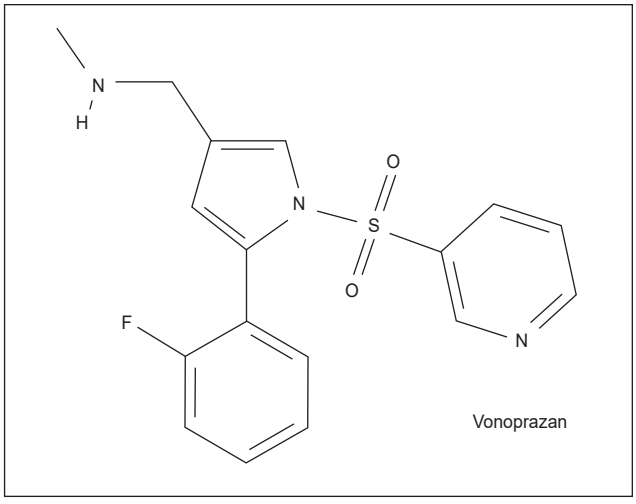
As a result, the activity of H^+,K^+-ATPase in the parietal cells is regulated by the availability of extracellular K^+. Studies on molecular mechanisms of H^+,K^+-ATPase, therefore, led to discovery of potassium-competitive acid blockers, which is a new class of antisecretory agents and a novel treatment in acid-related diseases. This class of drugs exhibits their antisecretory effects by competitively blocking availability of K^+ for H^+,K^+-ATPase[8].

VONOPRAZAN

Vonoprazan is a novel, orally active potassium-competitive acid blocker that has demonstrated rapid, potent and long-lasting gastric acid suppression. It has been approved in Japan and 14 other countries in Asia and South America for a number of years for the treatment of a variety of acid-related diseases[7].

Vonoprazan Structure

Vonoprazan is a potassium-competitive acid blocker with the chemical structure $C_{17}H_{16}FN_3O_2S$. It is a pyrrole derivative that binds to the potassium ion binding site on the gastric proton pump, preventing the pump from activating and blocking gastric acid secretion.



Vonoprazan

Vonoprazan Uses

The principal use of vonoprazan is in management of GERD. It binds and inhibits H^+,K^+-ATPase at the final step in the acid secretory pathway in gastric parietal cells and it has different mechanisms of action than conventional PPIs. It can inhibit the proton pump even in neutral environments with an inhibitory constant (Ki) of 10 nM at pH 7 and 3 nM at pH 6.5. It has stronger potential to inhibit the gastric proton pump than other potassium-competitive acid blocker and lansoprazole[7].

The treatment of acid peptic disease is based on providing symptomatic relief and enhancement of ulcer healing in affected area, i.e., esophagus, stomach and duodenum and to heal and maintain remission of erosive esophagitis. The aim of treatment is also to prevent complications and recurrence and to improve the quality of life[6,9]. The medical management of GERD comprises of lifestyle modifications and pharmacologic agents[10]. Lifestyle modifications to treat GERD should remain the first line of therapy and it includes weight loss, avoiding late night meals, elevating head of bed and steering clear of habits or foods that may worsen symptoms[11].

PHARMACODYNAMICS AND PHARMACOKINETIC

The half-life of vonoprazan dissociation by potassium chloride is 12.5 hours in isolated proton pumps. Vonoprazan has high affinity and slow clearance from gastric parietal cells, accumulating in both resting and stimulated conditions. The acid dissociation constant of vonoprazan is 9.37, which is higher than that of conventional PPIs and other potassium-competitive acid blockers. When vonoprazan is exposed to acidic conditions, it is instantly protonated and remains stable. It can accumulate, function, and bind the proton pump

of gastric parietal cells in strongly acidic secretory canaliculi. The dissociation rate of vonoprazan from H^+,K^+-ATPase is slow and acid does not decompose it. Nonionic type of vonoprazan is decreased in a strong acidic secretory canaliculi and passive transport from the acidic secretory canaliculus to the cytoplasm is inhibited. It is therefore retained for a long time inside the parietal cells and can inhibit H^+,K^+-ATPase that is activated by further stimulation of acid secretion. The concentration of vonoprazan is up to 10^8-fold higher in secretory canaliculus of parietal cell than in plasma. It can stay in the protonated form and binds to H^+,K^+-ATPase subunit to compete with potassium binding and inhibits function of pump. The binding of vonoprazan to the proton pump is ionic, and its effects are reversible and dose-dependent. Vonoprazan can be taken regardless of meal ingestion and the rate of absorption is not affected by meals. It is rapidly absorbed and the time taken to reach maximum concentration in plasma is less than 2 hours after oral administration. After absorption, the half-life in plasma is approximately 2 hours for conventional PPIs, but up to 9 hours for vonoprazan. Thus, vonoprazan stays in blood longer and can block acid secretion continuously[7].

Vonoprazan demonstrated noninferiority and superiority compared to PPI lansoprazole in both healing and maintenance of erosive esophagitis. This advantage was particularly notable in cases of more severe erosive esophagitis[12]. Vonoprazan has noninferior efficacy compared to lansoprazole in terms of erosive esophagitis healing rate[13]. Transitioning from a PPI to vonoprazan is significantly linked to symptom improvement in GERD patients resistant to PPI therapy. Hence, vonoprazan presents a promising treatment option for PPI-resistant GERD[14]. It significantly improved heartburn and patient satisfaction, among patients with PPI-resistant GERD[15]. Vonoprazan 20 mg shows a similar tolerability profile to lansoprazole 30 mg and is noninferior in terms of gastric ulcer healing. It also demonstrates similar efficacy for duodenal ulcer healing, despite not meeting the noninferiority criteria[16]. Vonoprazan 10-20 mg demonstrated efficacy comparable to lansoprazole 15 mg in preventing peptic ulcer recurrence during low-dose aspirin therapy, exhibited a similar long-term safety profile and was well-tolerated[17].

A vonoprazan-based regimen is more effective than a PPI-based regimen as a first-line *H. pylori* eradication therapy[18]. Vonoprazan triple therapy and vonoprazan quadruple therapy regimens demonstrated increased *H. pylori* eradication rates compared to traditional quadruple therapy. Vonoprazan triple therapy exhibited fewer side effects, suggesting its potential applicability for *H. pylori* eradication in clinical practice[19].

Vonoprazan Dosage and Administration

Vonoprazan film-coated tablets of 10 and 20 mg are available. They can be taken without regard to food or timing of food and should be swallowed and not chewed. The recommended dosage of vonoprazan is 20 mg once a day for 4 to 8 weeks in reflux esophagitis, 10 mg once a day for maintenance of healing esophagitis, 20 mg once a day for 8 weeks and 6 weeks for gastric and duodenal ulcers, respectively, 10 mg once a day for prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer and 20 mg twice daily with triple drug regimen for 1 week for *H. pylori* eradication.

Vonoprazan Contraindications

Vonoprazan is contraindicated in patients with known hypersensitivity to vonoprazan or any component of vonoprazan, rilpivirine containing products. As a precaution, vonoprazan should not be given during pregnancy and lactation.

Vonoprazan Side Effects

The side effects of vonoprazan include nausea, headache, dysgeusia, dyspepsia, gastritis, pain abdomen, abdominal distension, diarrhea, nasopharyngitis, vulvovaginal candidiasis, urinary tract infection, and hypertension.

CONCLUSION

Vonoprazan plays a significant role in management of acid peptic diseases, especially in the treatment of GERD, peptic ulcer disease and *H. pylori* infection. It causes potent acid suppression, rapid symptom relief and has better outcome as compared to traditional PPI therapies. Further, it can be given empty stomach as well as after meals.

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CASE REPORT

An Unusual Presentation of Splenic Rupture in a Hemodialysis Patient

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ABSTRACT

Splenic rupture, although rare in dialysis patients, can be life-threatening. In this case, a 45-year-old man with kidney failure on hemodialysis experienced sudden and severe abdominal pain in the left flank, without any history of trauma. He displayed symptoms of hypovolemic shock, characterized by pallor, hypotension, and tachycardia. Additionally, he had abdominal distension and tenderness. An abdominal CT scan revealed a splenic hematoma and intra-abdominal hemorrhage. The patient required a splenectomy to address the ongoing bleeding, but unfortunately, he succumbed to post-splenectomy sepsis 2 weeks later.

Keywords: Atraumatic, splenic rupture, hemodialysis, platelet dysfunction, kidney failure

Atraumatic splenic rupture is less common than trauma-related cases[1]. However, in dialysis patients, platelet dysfunction significantly increases the risk of bleeding from internal organs like the spleen[1]. Nontraumatic splenic rupture can also occur due to factors such as heparin use, infections, splenic infarction, amyloidosis, and portal hypertension[1-4].

Spontaneous splenic rupture is a potentially life-threatening condition and it is important to maintain a high level of suspicion in kidney failure patients experiencing abdominal pain and bleeding. In cases of hemodynamic instability, splenectomy may be necessary. However, it carries a risk of post-splenectomy sepsis. In this case, a patient with kidney failure, on hemodialysis, experienced spontaneous splenic rupture, but unfortunately developed post-splenectomy sepsis and passed away.

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CASE PRESENTATION

Medical History

A 45-year-old man with kidney failure due to chronic glomerulonephritis began hemodialysis in January 2024. He visited the emergency department with severe abdominal pain that had been ongoing for 8 hours. The pain started suddenly, was sharp, and rated as 10 on a scale of 1 to 10.

It was present throughout his abdomen, particularly severe on the left side, and worsened with movement. He had no prior history of left chest wall or shoulder pain, no previous instances of similar pain, and no abdominal injuries. He mentioned passing loose, watery stool before coming to the hospital but had not experienced vomiting, increased abdominal swelling, or a fever. About 1 month ago, he was treated for an anterior chest wall abscess, which had developed at the point of previous insertion of a subclavian venous catheter.

He had an incision and drainage and was treated with antibiotics in the outpatient clinic but did not return for a follow-up. He had been consistently receiving hemodialysis twice a week along with intradialytic doses of unfractionated heparin (5,000 IU).

For the past 2 months, he had been producing limited urine and developed ascites, requiring occasional abdominal paracentesis guided by ultrasound. Four days before his hospital visit, his packed cell volume was measured at 28% before his routine dialysis

session. He did not have diabetes and had not recently undergone surgery.

His regular medications included nifedipine, torsemide, hydralazine, metoprolol, iron sucrose, vitamins, and erythropoietin.

On examination, he was sweaty, pale, and in shock with pulse rate and blood pressure of 110 bpm and 97/54 mmHg, respectively. His pulse was weak but equal on both sides. The abdomen was distended and generalized abdominal tenderness, maximal in the left hypochondriac region, was present. There were no significant findings in other systems.

Initial differential diagnosis:

- Suspected abdominal aortic dissection
- Splenic rupture
- Spontaneous bacterial peritonitis.

Treatment

He was admitted to the high-dependency unit and started on intravenous noradrenaline. A blood transfusion of 4 pints of blood and 1 unit of fresh frozen plasma was urgently requested. He was also administered intravenous antibiotics (meropenem and metronidazole) and the general surgical team was promptly consulted for further assessment.

Oxygen therapy was initiated and he was advised nil per os. He underwent laparotomy, on Day 1 of admission which revealed a ruptured spleen with a subcapsular hematoma of approximately 2 liters and 2.5 liters of blood in his abdomen (hemoperitoneum) necessitating a splenectomy. He received an additional 5 units of blood and 2 units of fresh frozen plasma due to significant blood loss during surgery.

While on inotropic support, his pulse rate was 102 bpm and his blood pressure was 130/60 mmHg. He was not given heparin for his subsequent dialysis. He had pneumococcal and meningococcal vaccination on the 7th day of surgery as vital signs were stable and results were normal.

Outcome and Follow-Up

On the 13th day of surgery, he developed a massive upper gastrointestinal bleed and blood parameters were consistent with a disseminated intravascular coagulopathy from sepsis (see Table 1).

Thereafter, he received 4 units of fresh frozen plasma with blood and but bleeding did not stop. He succumbed to the illness on 15th day of surgery.

Table 1. Investigations

Test	Results
Full blood count	Hemoglobin – 3.3 g/L; Packed cell volume – 9.6%; Platelet – 2,67,000 cells/mm^3; White blood cell count – 12,000 cells/mm^3 (Neutrophil – 77.9%; Lymphocyte – 30%)
Abdominal CT scan	See Figure 1
Clotting profiles	
• At presentation	Prothrombin time (PT) – 10 seconds; Partial thromboplastin time with kaolin (PTTK) – 37 seconds
• At Day 14	PT – 16 seconds; PTTK – 50 seconds
Kidney function tests	
• At presentation	Sodium – 145 mmol/L; Potassium – 4.4 mmol/L; Urea – 21.3 mmol/L; Creatinine – 903 mmol/L
• At Day 14	Sodium – 138; Potassium – 3.9 mmol/L; Urea – 34.8 mmol/L; Creatinine – 385 mmol/L
	PT – 14 seconds; PTTK – 45 seconds, INR – 1
Splenic tissue histology	Normal splenic tissue with areas of cellular necrosis and inflammatory changes
D-dimer (Day 14)	3.67 µg/mL (0-0.5)
Peripheral blood film (Day 14)	Fragmented red blood cells with schistocytes and target cells. The white cells showed neutrophilia with toxic granulation. Platelets were normal, but reduced at 3-4 per high power field.

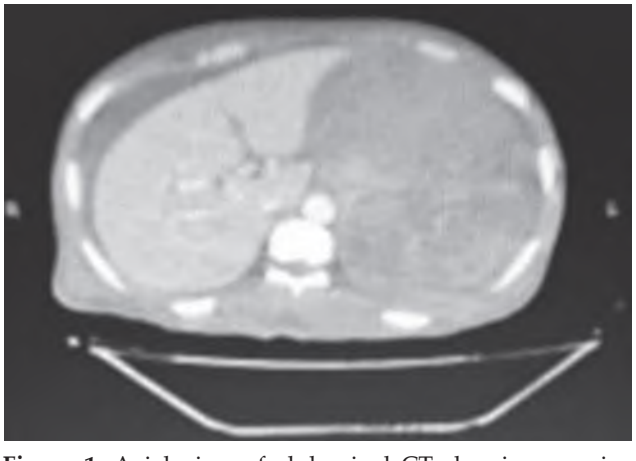

Figure 1. Axial view of abdominal CT showing massive splenic hematoma.

DISCUSSION

Atraumatic splenic rupture is a less common but potentially fatal cause of massive intra-abdominal hemorrhage. Splenic rupture can occur in a healthy spleen[5], although splenic injury from trauma is more prevalent. A systematic review of over 800 published cases identified the main causes of nontraumatic splenic rupture as malignancies, infections, and inflammatory diseases (30%, 27%, and 20%, respectively)[6,7].

Other causes included drugs (9%), mechanical causes such as pregnancy (7%), and unknown causes (7%)[6,7]. The mortality rate was 12%, with most deaths occurring in patients with splenomegaly, those over the age of 40, and those with malignancies[6,7]. Several mechanisms of splenic rupture have been postulated[8,9].

However, the most widely accepted explanations include raised intra-abdominal pressure due to contracting abdominal muscles during physical activities, intra-splenic cellular congestion, and increased fragility of splenic blood vessels resulting from infarctions and thromboses[8,9].

Spontaneous splenic rupture in dialysis patients is most frequently caused by uremic coagulopathy[8,10]. This condition is characterized mainly by platelet dysfunction, specifically a decrease in active integrin alpha IIb/beta 3 (formerly known as glycoprotein IIb/IIa), due to the accumulation of blood uremic toxins[11-13].

However, some other factors also contribute to this condition, for example, the use of antiplatelet medications, administration of heparin during dialysis, and anemia[13]. Splenic infarcts, thrombocytopenia, portal hypertension, and amyloidosis are also potential risk factors[14].

Conversely, the serum levels of pro-hemostatic clotting factors are generally normal or increased in chronic kidney disease, which may be prothrombotic[13].

Additionally, the reduced levels of naturally occurring anticoagulants such as protein C and S may also result in thrombosis in patients having nephrotic syndrome[13].

Therefore, strategies to prevent uremic bleeding should include optimization of hemodialysis, treatment of anemia, judicious use of medications such as anticoagulants and antiplatelets, and lastly administration of desmopressin before high-risk procedures[13,15].

Our patient had risk factors for uremic coagulopathy such as exposure to heparin, azotemia, and anemia. He had no other risk factor for splenic rupture. Due to the massive intraperitoneal hemorrhage and hemodynamic instability, he underwent splenectomy but developed post-splenectomy sepsis afterwards.

CONCLUSION

Splenic rupture should be considered in the differential diagnosis of abdominal pain with shock in a hemodialysis patient. Urgent investigation is needed for prompt surgical intervention.

Patients on hemodialysis who have had splenectomy are at risk of sepsis and have to be aggressively treated to prevent mortality.

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■■■■

BRIEF COMMUNICATION

Chronotype, Myokines, and Muscle Mass: A New Dimension in Metabolic Disorders

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Chronotype refers to an individual's innate preference for the timing of sleep-wake cycles and daily activities, which is governed by their circadian rhythm. People show distinct variations in their chronotype, primarily categorized by their inclination towards either morningness or eveningness, which affects sleep onset, wake time, and the timing of cognitive and physical activities (Table 1). Based on these preferences, individuals can be classified as morning types, evening types, or intermediate types. Notably, this preference for morning or evening activity is a relatively stable characteristic influenced by intrinsic factors.

At the population level, an evening chronotype is independently linked to an increased risk of metabolic syndrome and diabetes. Evening chronotype has been associated with metabolic irregularities and changes in body composition in middle-aged adults, even when controlling for factors like sleep duration and lifestyle. People with an evening chronotype tend to have higher fat mass and lower lean mass compared to those with a morning chronotype. These effects on body fat and lean mass are found to be independent of obesity. Studies show that individuals with an evening chronotype have a significantly higher mean percentage of body fat, while those with a morning chronotype tend to have a higher percentage of lean mass[1].

Several factors may be responsible for this association between chronotype and body composition. Melatonin, a pineal hormone entrained in the 24-hour environmental light-dark cycle, is a reliable circadian system marker and its levels peak at night. Melatonin is suppressed by light; thus, individuals with evening chronotype who have greater exposure to light at night, are likely to have lower melatonin levels. Low melatonin levels have been shown to contribute to muscle loss, primarily by affecting oxidative stress and muscle regeneration processes, leading to an increased risk of muscle degradation and atrophy, leading to a lower muscle mass[2,3]. Patients with evening chronotype are more likely to take afternoon naps. Habitual daytime napping is associated with adverse health outcomes such as metabolic disorders and sarcopenia[4].

Individuals with an evening chronotype tend to exhibit a higher body mass index (BMI) and increased plasma C-reactive protein (CRP) levels. They also demonstrate a stronger cortisol response when subjected to stress. Glucocorticoids play a role in regulating lipid metabolism in both adipose tissue and the liver, while also promoting hepatic gluconeogenesis and peripheral insulin resistance. Prolonged activation of the hypothalamic-pituitary-adrenal axis and an elevated cortisol secretion can lead to the accumulation of visceral fat and an increase in body weight. The combination of higher CRP levels and an intensified cortisol response may contribute to the elevated risk of metabolic disorders in individuals with an evening chronotype.

Testosterone levels, are expected to be highest in the morning but they may peak later in the day for individuals with evening chronotype. Testosterone has a role in maintaining muscle mass by promoting muscle protein synthesis. This delayed testosterone peak in evening chronotypes can affect the timing of muscle repair and growth, potentially leading to reduced anabolic effects on skeletal muscle, lower muscle mass, and reduced skeletal strength[5].

Shift work, particularly among individuals with an evening chronotype are at higher risk of adverse changes in body composition and metabolic health. Shift workers with evening chronotypes exhibit a higher propensity for increased adiposity and unfavorable body composition, including elevated fat mass and reduced lean muscle mass[6]. This might be mediated by poor sleep quality, irregular eating patterns, and elevated cortisol levels, which further exacerbate metabolic disturbances. It has been observed that evening chronotypes tend to engage

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Table 1. Chronotype, Body Composition and Risk of Metabolic Disorders

Characteristic	Morning chronotype	Intermediate chronotype	Evening chronotype
Sleep-Wake pattern	Wake up early in the morning and go to sleep early at night Higher energy levels in the morning	Follow a moderate schedule	Wake up late in morning and go to sleep late at night Higher energy levels in the evening
Body composition	Lower fat mass, higher lean mass	Balanced body composition	Higher fat mass, lower lean mass
Risk of metabolic disorders	Lower risk	Moderate risk	Higher risk
Metabolic signature	Lower TG, higher HDL-C, lower HOMA-IR	Intermediate TG, intermediate HDL-C, intermediate HOMA-IR	Higher TG, lower HDL-C, higher HOMA-IR
Hormonal signature	Normal cortisol response to stress, normal testosterone peak, higher melatonin	Strong cortisol response to stress, normal testosterone peak, intermediate melatonin	Stronger cortisol response to stress, delayed testosterone morning peak, lower melatonin

TG = Triglycerides; HDL-C = High-density lipoprotein cholesterol; HOMA-IR = Homeostasis model assessment of insulin resistance.

in behaviors such as higher alcohol consumption and erratic meal timing, contributing to unhealthy body composition[7].

Skeletal muscle secretes signaling molecules known as myokines, which interact with other organs and play a crucial role in regulating muscle mass and function. Myokines mediate the positive effects of muscle mass and physical activity on overall health[8]. For instance, myostatin, a specific myokine, is secreted in greater amounts from the muscles of obese individuals. Myostatin mRNA levels are lower in those without sarcopenia than in those with the condition. Increased myostatin expression in both muscle tissue and plasma correlates with greater insulin resistance and is linked to higher levels of intramuscular fat in the mid-thigh region. Elevated myostatin in muscle acts as a negative regulator of muscle growth, resulting in decreased lean body mass[9,10]. Conversely, irisin, another myokine, is released by contracting skeletal muscles and is associated with beneficial effects. Low circulating irisin levels are a marker of muscle weakness and atrophy, while higher levels promote muscle growth and the browning of white adipose tissue, leading to better body composition with reduced fat and increased muscle mass. Levels of myokines have shown association with insulin resistance and risk of metabolic disorders such as type 2 diabetes and metabolic syndrome[11,12].

While the greater lean mass in morning chronotype, has been attributed to higher levels of physical activity, it is possible that myokines may mediate the muscle accumulation in individuals. The skeletal muscles have their own intrinsic clock and this clock may have an impact on secretion of myokines.

Unravelling these aspects of chronotype, skeletal muscle clocks, and myokines may open up newer diagnostic and therapeutic modalities for metabolic disorders. In future, the diagnosis of sarcopenia may be objectively confirmed from myokine profiles. Resetting of muscle clock or exogenous administration of myokines may be potential therapeutic options for increasing lean mass and reducing fat mass. In face of the onslaught of metabolic disorders, myokines and chronotype may prove to invaluable management options in the near future.

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Nutrition for Optimal Immune System Health

VIRENDRA KUMAR GUPTA

Adequate and appropriate nutrition is vital for optimal functioning of all cells, including immune cells[1]. Optimal nutrition helps immune cells initiate effective responses against pathogens, respond rapidly when needed and prevent chronic inflammation[1].

Certain micronutrients and dietary components play specific roles in developing and maintaining an effective immune system and reducing chronic inflammation[1].

Excessive intake of certain micronutrients can also impair immune responses, such as iron supplementation increasing morbidity and mortality in malaria-endemic regions[1].

GUT-ASSOCIATED LYMPHOID TISSUE

The gut-associated lymphoid tissue (GALT) houses a majority of immune cells in the human body, underscoring its significance in maintaining overall host health[1]. The gut lumen contains the human gut microbiome, which provides antigens and signals that can interact with local and systemic immune cells[1]. The composition of the gut microbiome changes throughout life in response to dietary factors and environmental influences like antibiotic use[1].

Several nutrients and dietary interventions have shown promising effects in improving gut health and reducing inflammation[1]. The Mediterranean diet, characterized by consuming vegetables, fruits, nuts, legumes, fish, and healthy fats, has been associated with a lower risk of chronic diseases such as cardiovascular disease, cancer and Alzheimer's disease[1]. Fruits and vegetables contain bioactive compounds, including dietary polyphenols, that have immunomodulatory and anti-inflammatory properties[1].

THE MINERALS ZINC AND SELENIUM

Zinc is a cofactor in numerous proteins, and even a mild deficiency can impair both the adaptive and innate immune response. During sepsis, zinc homeostasis is disrupted, which has implications for therapeutic strategies in septic patients[1].

Selenium plays crucial functional, structural, and enzymatic roles in various proteins, and maintaining optimal selenium status is vital for immune function and reducing the risk of chronic diseases such as cancer and cardiovascular disease[1].

VITAMINS

Vitamin A plays a crucial role in regulating both innate and cell-mediated immunity[2]. Its deficiency leads to increased susceptibility to infections and impaired immune function[2]. Vitamin A deficiency affects cytokine release, antibody production and the function of various immune cells[2]. Vitamin A promotes the expansion and differentiation of Th1 and Th2 cells, regulating the balance between proinflammatory and anti-inflammatory responses[2]. Retinoic acid, a form of vitamin A, is involved in numerous biological activities and can impact intestinal inflammation and macrophage activity[2]. Vitamin A administration has been beneficial in reducing mortality from diarrheal diseases and has shown potential antitumor effects in various cancers[2].

The B vitamins, including B1, B2, B3, and B12, play essential roles as co-enzymes in various metabolic pathways and cellular functions[2]. Vitamin B1 or thiamine, has antioxidant properties and can inhibit cytokine synthesis and antimicrobial oxidative reactions[2]. It regulates immune metabolism by balancing glycolysis and the tricarboxylic acid cycle[2]. Deficiency in vitamin B1 can lead to proinflammatory cytokine expression, neuroinflammation and neuronal death[2]. Thiamine has potential therapeutic applications in neurodegenerative diseases[2].

Riboflavin (vitamin B2) exhibits anti-inflammatory and antioxidant properties and activates mucosa-associated invariant T cells[2].

Vitamin B3 (niacin) functions as a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) cofactors involved in redox reactions, and it has anti-inflammatory effects through inhibition of the nuclear factor-kappa B pathway[2].

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Vitamin B12 (cobalamin) affects pro- and anti-inflammatory responses, and its deficiency is associated with altered immune cell populations, hyperhomocysteinemia, insulin resistance and potential links to certain cancers[2].

Vitamin C acts as an antioxidant, regulates immune functions and has anti-inflammatory properties[2]. It can inhibit proinflammatory cytokines, enhance anti-inflammatory markers, modulate immune cell activity and potentially aid in the defense against microbial pathogens[2].

Vitamin D exerts anti-inflammatory effects through its interaction with receptors and signaling pathways[2]. It can inhibit proinflammatory cytokines, regulate immune cell responses and contribute to the defense against infections[2]. Additionally, vitamin D has been associated with anticancer effects, including apoptosis stimulation, suppression of cancer cell proliferation and inhibition of proinflammatory signaling pathways[2].

MACRONUTRIENTS

Arginine, an amino acid, is crucial to immune system function[2]. It is involved in producing nitric oxide, which is important for macrophages in combating pathogens. They also play a role in the regulation of cytotoxicity by macrophages and have implications for pathogen recognition[2]. The enzyme arginase-1 (Arg-1) may be involved in reducing inflammation through its anti-inflammatory action[2].

Tryptophan is essential for the activity of the immune system[2]. Tryptophan metabolism and its metabolites can influence immune signaling and metabolic pathways, and the balance between kynurenine and tryptophan can have anti-inflammatory effects[2]. The kynurenine pathway regulates inflammation, mediated by enzymes such as indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. The kynurenine/tryptophan ratio may be a marker for inflammation in various conditions[2].

Glutamine, a nonessential amino acid, is an energy source and precursor for nucleotide synthesis, vital for rapidly dividing immune cells during immune responses[1]. It plays a role in the functions of immune cells and is depleted in critical illness, highlighting the potential for clinical nutrition supplementation in critically ill patients[1].

THE ROLE OF CHOLESTEROL AND FATTY ACIDS IN THE IMMUNE RESPONSE

Cholesterol plays a critical role in immune responses, particularly in the functionality of cellular membranes, especially the plasma membrane[2]. It is essential for maintaining membrane integrity, fluidity and receptor arrangement. An imbalance in cholesterol levels can lead to the deposition of lipid plaques, triggering an inflammatory process[2].

Omega-3 fatty acids eicosapentaenoic acids and docosahexaenoic acids are essential for promoting the resolution of inflammation, including in the respiratory tract[3]. Consuming an adequate amount of these fatty acids produces anti-inflammatory metabolites, which help alleviate inflammation[3].

In conclusion, nutrition and immune function have a strong and dynamic relationship[2]. Nutrients are crucial in modulating immune function through pro-inflammatory and anti-inflammatory effects[2]. Micronutrients such as vitamins A, B1, B2, B3, B12, C, and D; and minerals like zinc and selenium can influence both innate and adaptive immunity through genetic, biochemical, and signaling pathways[2]. These nutrients can impact immune cells' proliferation, cell division, mobilization, and overall physiology[2].

Furthermore, certain macronutrients like tryptophan, arginine, cholesterol, and polyunsaturated fatty acids have also been implicated in preventing and treating immune-related diseases[2].

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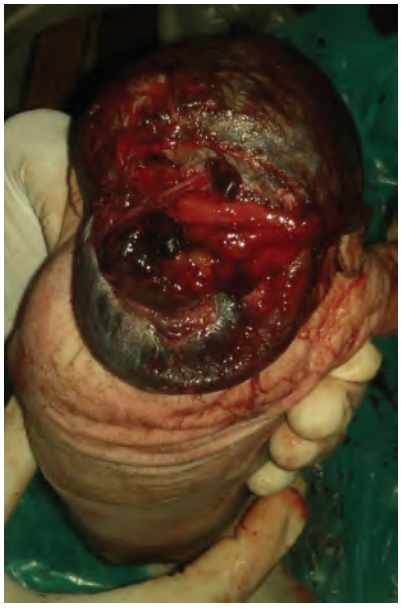
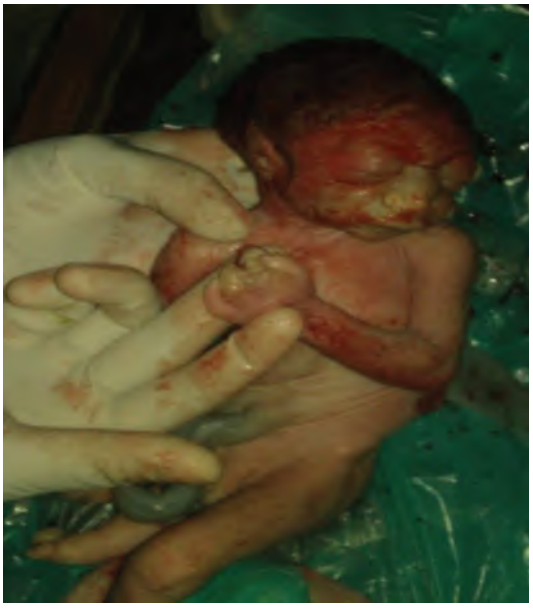
PICTURE QUIZ

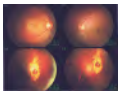
What is the Diagnosis?

a) Meckel-Gruber syndrome
b) Microcephaly
c) Polydactyly
d) All of the above



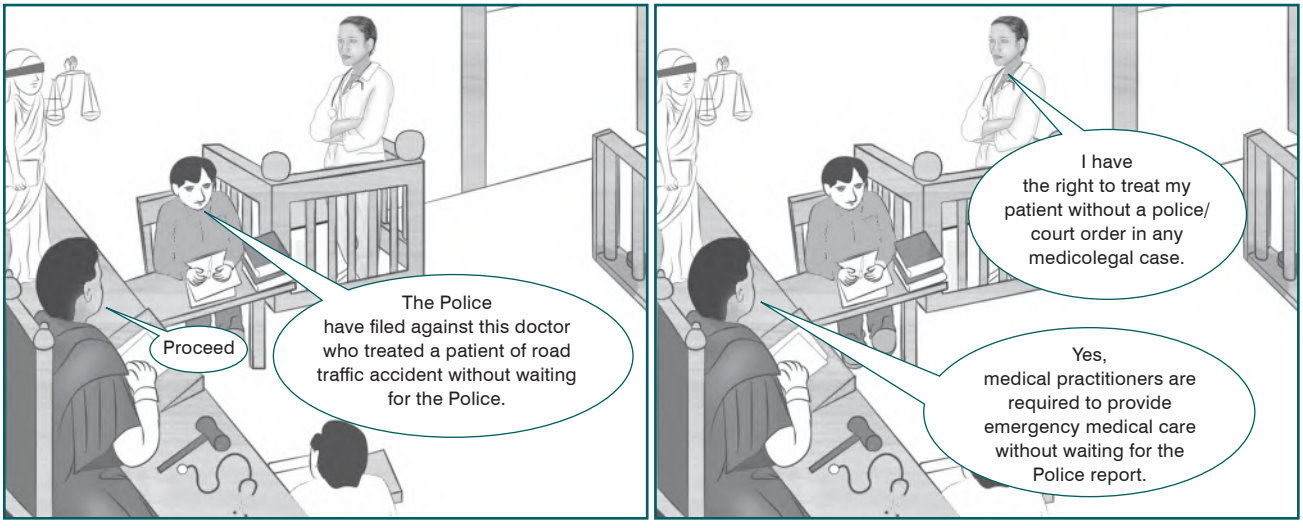


Answer to the Picture Quiz from the Indian Journal of Clinical Practice, Vol. 35, No. 8, January 2025

Answer: (a) 

See Answer in the Next Month's Issue!

Doctors are Required to Provide Emergency Medical Care without Waiting for the Police Report



Lesson: Doctors have the right to practice unencumbered in the best interest of patients even in medicolegal cases. In Pt. Parmanand Katara vs Union Of India & Ors on 28 August, 1989 AIR 2039, 1989 SCR (3) 997, the Supreme Court of India, in the context of medicolegal cases, has emphasised the need for rendering immediate medical aid to injured persons to preserve life and the obligations of the State as well as doctors in that regard. The Court observed: "Every doctor whether at a Government Hospital or otherwise has the professional obligation to extend his services with due expertise for protecting life. No law or State action can intervene to avoid/delay the discharge of the paramount obligation cast upon members of the medical profession." Regulation 13 of the Code of Medical Ethics framed by the Medical Council of India also says that the patient must not be neglected. "A physician is free to choose whom he will serve. He should, however, respond to any request for his assistance in an emergency or whenever temperate public opinion expects the service…"

CASE SUMMARY

Mr P, a human rights activist, filed a writ petition in the Supreme Court under Article 32 of the Constitution of India on the basis of a newspaper report titled ''Law helps the injured to die". According to the story, a bystander picked up an injured scooterist who had been hit by a speeding car. He took the injured to the hospital nearby, but the doctors refused to attend to the victim and instead asked him to take the injured person to another hospital located, 20 km away, that was authorised to handle medicolegal cases.

The victim succumbed to his injuries before he could reach the hospital. Mr 'P' asked that every citizen brought to the hospital should be promptly administered treatment and the procedural criminal law should be allowed to operate after that. And, suitable compensation should be allowed in addition to any action taken for negligence in contravention of this directive.

SOME SALIENT COURT OBSERVATIONS

- The Counsel for Medical Council of India (MCI) stated that there is no prohibition in law to justify the attitude of doctors as complained. The affidavit filed on behalf of the MCI mentioned 'Clause 10 – Obligations to the sick and Clause 13 – The patient must not be neglected' of the Code of Medical Ethics Regulations and further stated: "*… It should be the duty of a doctor in each and every casualty department of the hospital to attend such person first and thereafter take care of the formalities under the Criminal Procedure Code. The life of a person is far more important than the legal formalities.*"
- The affidavit filed on behalf of the Union of India on 3rd August, 1989 also said: "*There are no provisions in the Indian Penal Code, Criminal Procedure Code, Motor Vehicles Act, etc. which prevent Doctors from promptly attending seriously injured persons and accident case before the arrival of Police and their taking*

into cognisance of such cases, preparation of F.I.R. and other formalities by the Police."

- *"There can be no second opinion that preservation of human life is of paramount importance. This is so on account of the fact that once life is lost, the status quo ante cannot be restored, as resurrection is beyond the capacity of man."*
- *"Every doctor whether at a Government hospital or otherwise has the professional obligation to extend his services with due expertise for protecting life. No law or State action can intervene to avoid/delay the discharge of the paramount obligation cast upon members of the medical profession. The obligation being total, absolute and paramount, laws of procedure whether in statutes or otherwise which would interfere with the discharge of this obligation cannot be sustained and must, therefore, give way."*
- *"There is also no doubt that the effort to save the person should be the top priority not only of the medical professional but even of the Police or any other citizen who happens to be connected with the matter or who happens to notice such an incident or a situation."*
- The Court observed that there is an apprehension among doctors that they would be called as witness in medicolegal cases and also that they would be interrogated by the Police, which prevents them from helping such cases. It said, *"…, the policy, the members of the legal profession, our law courts and everyone concerned will also keep in mind that a man in the medical profession should not be unnecessarily harassed for purposes of interrogation or for any other formality and should not be dragged during investigations at the Police station and it should be avoided as far as possible. We also hope and trust that our law courts will not summon a medical professional to give evidence unless the evidence is necessary and even if he is summoned, attempt should be made to see that the men in this profession are not made to wait and waste time unnecessarily…"*
- *"We have no hesitation in saying that it is expected of the members of the legal profession which is the other honourable profession to honour the persons in the medical profession and see that they are not called to give evidence so long as it is not necessary… where the facts are so clear it is expected that necessary harassment of the members of the medical profession either by way of requests for adjournments or by cross examination should be avoided so that the apprehension that the men in the medical profession have which prevents them from discharging their duty to a suffering person who needs their assistance utmost, is removed and a citizen needing the assistance of a man in the medical profession receives it."*
- *"…if he finds that whatever assistance he could give is not sufficient really to save the life of the person but some better assistance is necessary-it is also the duty of the man in the medical profession so approached to render all the help which he could and also see that the person reaches the proper expert as early as possible."*

COURT ORDER

The Court ordered that the guidelines indicated in the 1985 decision of the Committee under the Chairmanship of the Director-General of Health Services should become operative.

1. *"Whenever any medicolegal case attends the hospital, the medical officer on duty should inform the Duty Constable, name, age, sex of the patient and place and time of occurrence of the incident, and should start the required treatment of the patient. It will be the duty of the Constable on duty to inform the concerned Police Station or higher police functionaries for further action. Full medical report should be prepared and given to the Police, as soon as examination and treatment of the patient is over. The treatment of the patient would not wait for the arrival of the Police or completing the legal formalities.*

2. *Zonalisation as has been worked out for the hospitals to deal with medicolegal cases will only apply to those cases brought by the Police. The medicolegal cases coming to hospital of their own (even if the incident has occurred in the zone of other hospital) will not be denied the treatment by the hospital where the case reports, nor the case will be referred to other hospital because the incident has occurred in the area which belongs to the zone of any other hospital. The same police formalities as given in para 1 above will be followed in these cases.*

   All Government Hospitals, Medical Institutes should be asked to provide the immediate medical aid to all the cases irrespective of the fact whether they are medicolegal cases or otherwise. The practice of certain Government institutions to refuse even the primary medical aid to the patient and referring them to other hospitals simply because they are medicolegal cases is not desirable. However, after providing the primary medical aid to the patient, patient can be referred to the hospital if the expertise facilities required for the treatment are not available in that Institution."

REFERENCE

1. Pt. Parmanand Katara vs Union of India & Ors on 28 August, 1989; 1989 AIR 2039, 1989 SCR (3) 997.

DRS-WCPD: 11th World Congress on Prevention of Diabetes and Its Complications

PREVENTION OF HEART FAILURE IN DIABETES

Dr PC Manoria, Bhopal

- Human myocytes do not have an endogenous capacity for repair; once dead, they cannot regenerate.
- Preventing heart failure (HF) is critical, as it follows a malignant progression once it sets in and is associated with high mortality and morbidity.
- Serum biomarkers like B-type natriuretic peptide (BNP) >50 pg/mL and N-terminal pro-BNP (NT-proBNP) >135 pg/mL should be included in the assessment of stages A and B of HF.
- The prevention of HF in clinical practice is often neglected, highlighting an urgent need to promote current scientific knowledge on HF prevention in stages A and B.

LINAGLIPTIN/DAPAGLIFLOZIN/METFORMIN FDC: THE NEW KID ON THE BLOCK

Dr L Sreenivasa Murthy, Bengaluru

Approximately 67% of type 2 diabetes mellitus (T2DM) patients in India do not meet their target glycated hemoglobin (HbA1c) goals. As a multifactorial disease with significant cardiorenal complications, T2DM requires the use of oral antidiabetic drugs that address multiple pathophysiological defects to achieve effective glycemic control.

Delayed treatment intensification in high-risk patients increases the likelihood of myocardial infarction and stroke. Research indicates that early, intensive glycemic control can reduce the risk of both micro- and macrovascular complications. According to the American Diabetes Association (ADA) guidelines, combination therapy is recommended when HbA1c is ≥1.5% above target levels.

The fixed-dose combination (FDC) of metformin, dapagliflozin, and linagliptin improves glycemic control and addresses cardiorenal complications, reflecting real-world clinical practices. This once-daily regimen targets a wide range of pathophysiological factors involved in hyperglycemia, improving patient compliance, and quality of life.

Key Observations

- Combination therapy addresses multiple pathophysiological defects, achieving significant HbA1c reduction while minimizing pill burden.
- Combining dapagliflozin and linagliptin with metformin offers clinically meaningful improvements in glycemic control with better tolerability and safety.
- Studies have shown that the triple combination of linagliptin, dapagliflozin, and metformin not only provides glycemic efficacy but also enhances cardiorenal safety. Additionally, linagliptin does not require routine monitoring of urine albumin-to-creatinine ratio (UACR) and does not need dose adjustments.
- The triple combination of metformin, dapagliflozin, and linagliptin can be used safely in patients with an estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m^2.

LADA: A MYSTERY SOLVED

Dr Narayan Deogaonkar, Nashik

- Latent autoimmune diabetes in adults (LADA) exhibits characteristics of both type 1 diabetes mellitus (T1DM) and T2DM.
- Early diagnosis is crucial for initiating the appropriate treatment and preventing complications.
- Clinicians should consider screening for LADA in patients with T2DM who do not achieve adequate glycemic control despite adhering to therapy.
  - Especially if they are not obese, lack features of metabolic syndrome, or have a personal or family history of autoimmune disorders.
- Recent insights into LADA's pathophysiology reveal that beta-cell destruction progresses slowly.
- A C-peptide test, whether basal or after a mixed meal, can be an initial, cost-effective screening tool to identify patients needing further confirmatory testing for islet autoantibodies.
- Insulin and dipeptidyl peptidase-4 (DPP-4) inhibitors, either alone or in combination with insulin,

thiazolidinediones, and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated effectiveness in achieving glycemic control and preserving beta-cell function.

REASSURING HYPERTENSION MANAGEMENT WITH CV PROTECTION IN YOUNG

Dr Anuj Maheshwari, Lucknow

Hypertension is a key risk factor for a range of cardiovascular conditions, such as coronary artery disease, left ventricular hypertrophy, valvular heart disease, atrial fibrillation, stroke, and renal failure. The continuous correlation between blood pressure levels and cardiovascular events blurs the distinction between high normal blood pressure and hypertension, as the cut-off values are somewhat arbitrary. Prevention and treatment of cardiovascular disease should be based on a comprehensive assessment of overall cardiovascular risk, which can be estimated using various models. However, age heavily influences risk categorization. Young adults, particularly women, may not be classified as high-risk despite having several major risk factors, emphasizing the importance of age-adjusted models. These models should evaluate relative risks compared to peers of the same age and incorporate assessments of target organ damage and 24-hour ambulatory blood pressure monitoring.

Key strategies for cardiovascular protection include:

- Managing dyslipidemia in young hypertensive patients with statins and following aspirin guidelines for primary prevention.
- Regularly monitor blood pressure at home and in clinical settings, as well as track kidney function, ECGs, and echocardiograms.
- Addressing barriers such as cost and side effects, utilizing educational strategies, simplified treatment regimens, and mobile apps to enhance patient outcomes can improve adherence.
- Leveraging digital health technologies, such as noninvasive blood pressure measurement devices and data storage systems, which are expected to play an increasing role in hypertension management, will improve both care and adherence.
- The continued use of existing antihypertensive medications, which are effective and well-tolerated.
- Expanding the use of free and fixed-drug combinations, such as spironolactone and other mineralocorticoid receptor antagonists.
- Considering medications initially developed for HF and diabetes that also have blood pressure-lowering effects.

LIVER AS A TARGET FOR PREVENTING DIABETES

Dr Bijay Patni, Kolkata

The liver is pivotal in glucose metabolism, managing blood sugar levels through glycogenesis and gluconeogenesis. It stores excess glucose as glycogen and releases it when necessary. Impaired liver function can disrupt glucose homeostasis and contribute to diabetes development. Research indicates that early detection and targeted treatment of nonalcoholic fatty liver disease (NAFLD) could help prevent T2D. Hence, liver-focused preventive strategies present a promising approach to tackling the diabetes epidemic.

Some effective pharmacological and nonpharmacological preventive measures include:

- Certain medications, such as GLP-1 agonists (e.g., liraglutide, semaglutide) and sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g., empagliflozin, canagliflozin), have demonstrated promising results in enhancing liver health and lowering diabetes risk.
- Ongoing clinical trials are exploring novel therapies, including farnesoid X receptor (FXR) agonists and apoptosis signal-regulating kinase 1 (ASK1) inhibitors, for treating NAFLD and preventing diabetes.
- Supplements like vitamin E and pioglitazone might also improve liver health and reduce diabetes risk, though further research is needed.
- Medications such as metformin and peroxisome proliferator-activated receptor (PPAR) agonists, especially PPAR-γ, show potential. These agents enhance insulin sensitivity and liver histology by reducing proinflammatory cytokines and increasing adiponectin production.
- A healthy diet, such as the Mediterranean diet, can help decrease liver fat and improve insulin sensitivity.
- Regular physical activity, including brisk walking or moderate-intensity exercise, reduces liver fat and enhances overall metabolic health.
- Maintaining or achieving a healthy weight is essential for improving insulin sensitivity and lowering the risk of NAFLD and T2D.

■■■■

News and Views

Long-Term Outcomes of Severe Childhood Asthma

Among adults aged 65 years and older, who had severe asthma in childhood, only 1 in 10 achieved asthma remission, while 1 in 3 experienced persistent airflow limitation, according to a 60-year follow-up study of adults with a history of severe childhood asthma published in the journal *Chest*[1].

A 60-year follow-up study was conducted with individuals with a documented history of severe childhood asthma to evaluate their disease characteristics in adulthood. The study included Danish adults who had a history of severe asthma during childhood and had undergone a 4-month stay at an asthma care facility in Kongsberg, Norway, between 1950 and 1979. After an average follow-up of 60 years, the patients were assessed via questionnaires and laboratory tests, spirometry, fractional exhaled nitric oxide (FeNO), bronchodilator reversibility, bronchial provocation with mannitol, and measurements of static lung volumes. Written informed consent was obtained from all participants. Patients in remission had not used any asthma medication and had been asymptomatic within the past 1 year. The others were categorized as having current asthma.

A total of 1,394 individuals were eligible for the study; of these, 232 completed the follow-up. Their mean age was 66.1 years. Among these, 89.7% had current asthma and 10.3% were classified as having asthma remission. Twenty-six percent reported experiencing exacerbations within the previous year; 21.6% had been treated with antibiotics for lower airway infection. Only 15.7% of all the participants were managed in secondary care.

Almost all the participants with current asthma were receiving inhaled controller therapy (83%). And two-thirds of those with current asthma used short-acting β_2-agonists as reliever, while others used long-acting β_2-agonists, inhaled corticosteroids (ICS), or long-acting muscarinic antagonists.

Sixty percent of those having current asthma had allergic rhinitis; 21% had hypertension, 16% had eczema, and 8% had cataract. Participants with persistent asthma had significantly higher total IgE levels, lower forced expiratory volume (FEV1)% predicted, and a reduced FEV1/FVC (forced vital capacity) ratio compared to those in remission. They also showed numerically higher levels of FeNO (26.7 vs. 20.1 ppb) and blood eosinophil count (0.19 vs. 0.17 10^9/L).

The definition of asthma remission used in this study emphasizes symptom management and medication use in the previous 12 months, recognizing asthma management from the patient's perspective. It considers how individuals perceive their symptoms and acknowledges that the treatment they report through questionnaires may differ from the prescribed treatment. This study offers valuable insights into the long-term prognosis of severe childhood asthma. It showed that nearly 90% of patients with a history of severe childhood asthma continued to have asthma during adulthood at a mean age of 66 years. Those with persistent asthma exhibited impaired lung function and elevated levels of type 2 inflammatory biomarkers compared to the 10% in remission. Hence, severe childhood asthma is a risk factor for potentially debilitating lung disease later in life.

Reference

1. Savran O, et al. Characteristics of adults with severe asthma in childhood: a 60-year follow-up study. Chest. 2024;166(4):676-84.

UACR: A Risk Factor for Adverse Cardiovascular Outcomes in Type 2 Diabetes?

A raised urinary albumin-to-creatinine ratio (UACR), even within the normal range, is associated with a higher risk of major adverse cardiovascular events (MACE) and total mortality in patients with type 2 diabetes. These findings from a study were published in the April 2024 issue of the *Journal of Clinical Endocrinology & Metabolism*[1].

A post hoc analysis of 10,171 participants from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and its follow-up study, ACCORDION was conducted to investigate the association between UACR and cardiovascular outcomes and mortality in patients with type 2 diabetes. These participants had baseline UACR data available. UACR is often used as a marker for kidney damage in diabetic patients. Univariate and multivariate Cox proportional hazard regression analyzes were conducted to examine the association between UACR and the risk of MACE and total mortality. The study also assessed the additional predictive value of UACR beyond other known risk factors for MACE and total mortality. Similar methods were used to analyze the correlation between UACR and MACEs and total mortality within the normal range.

Over the 8.83 years (median) of follow-up, a substantial proportion of participants experienced MACE and total mortality. Out of the 10,171 participants, 1,808 (17.78%) experienced MACE (nonfatal myocardial infarction, nonfatal stroke), and 1,934 (19.01%) died during the follow-up period. After adjusting for traditional cardiovascular risk factors, a significant association between UACR and the risk of both MACE and total mortality was seen on multivariate analysis. Importantly, the inclusion of UACR in the conventional risk model improved the predictive efficacy for both MACE and total mortality. Participants with elevated UACR had higher systolic and diastolic blood pressure (BP), glycosylated hemoglobin (HbA1c), triglycerides, very-low-density lipoprotein (VLDL) cholesterol and lower high-density lipoprotein (HDL) cholesterol.

According to this research, patients with T2DM who have a UACR of 10 to 30 mg/g are more likely to experience MACE and to die than those whose UACR is <10 mg/g. This study therefore suggests that UACR might be a sensitive marker for identifying individuals at increased risk, even if their UACR levels were within a clinically accepted normal range, which is taken to be below 30 mg/g. Hence, UACR values should be considered alongside traditional cardiovascular risk factors in clinical practice for risk assessment. "Early assessment of the UACR in patients with T2DM is important" suggest the authors. By doing so, health care providers may be better able to identify high-risk individuals and tailor interventions accordingly to mitigate the risk of adverse cardiovascular events and mortality in their patients with type 2 diabetes.

Reference

1. Zeng C, et al. Association of urine albumin to creatinine ratio with cardiovascular outcomes in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2024;109(4):1080-93.

Impact of Induction Timing on Maternal and Neonatal Outcomes

About half of the women with prelabor rupture of membrane (PROM) experience spontaneous labor following induction of labor at 24 hours compared to 12 hours. But they were at higher risk of chorioamnionitis, suggests a retrospective study published in the *American Journal of Obstetrics & Gynecology*[1].

This study was conducted at a single tertiary center between 2020 and 2023 to investigate the maternal and neonatal morbidity outcomes between induction of labor at 12 hours in 802 women versus 24 hours in 962 women following PROM. Women presenting with complications necessitating immediate delivery and multiple pregnancies were excluded from the study group. The study protocol was updated on July 1, 2021 to extend the conservative management duration by administering oxytocin after 24 hours instead of 12 hours post-PROM. The rate of chorioamnionitis was compared between two induction protocols for women at term with PROM and who did not show signs of active labor upon admission. Several differences were observed between the two groups. Half of the women (50.4%) in the 24-hour protocol group experienced spontaneous labor compared to the 12-hour protocol group (41.5%). They also had a higher rate of chorioamnionitis (7.5% vs. 4.7%). Cesarean deliveries occurred at similar rates between the two groups (16.3% vs. 17%). A higher percentage of neonates born after the 24-hour protocol required intensive care with neonatal intensive care unit admission rate of 6.2% vs. 3.6% in the 12-hour protocol group. They also required more antibiotics (5.7% vs. 2.9%) and also experienced respiratory distress (4.2% vs. 1.0%).

In the study, it was observed that among women with a previous vaginal delivery, the rate of inductions was lower following the 24-hour protocol compared to the 12-hour protocol (46.5% vs. 57.3%). However, maternal and neonatal outcomes were found to be similar between the two groups. On the other hand, among women with a previous cesarean delivery, the rates were lower following the 24-hour protocol compared to the 12-hour protocol, for oxytocin use (20.3% vs. 43.2%) and cesarean delivery (28.9% vs. 48.6%).

These findings suggest potential differences in induction practices and maternal and neonatal outcomes based on previous delivery history. These have potential implications for the management of term PROM. Hence, "shared decision-making" is crucial in the management of term PROM, state the authors. Women should be informed about the lower chance for induction and the higher risk of chorioamnionitis associated with the 24-hour induction protocol. They further suggest that parous women and those with a history of previous cesarean delivery may benefit from longer expectant management. Hence, past delivery history must be taken into consideration when making management decisions for term PROM.

Reference

1. Shqara RA, et al. 97: Induction of labor at 12 vs. 24-hours for prelabor rupture of membranes: a retrospective study. Am J Obstet Gynecol. 2024;230(1 Suppl):S71.

COPD: A Potential Risk Factor for Herpes Zoster

Persons with chronic obstructive pulmonary disease (COPD) nearly three times more likely to develop herpes

zoster (HZ) compared to those without COPD, according to a study published in the *Clinical Respiratory Journal*[1].

In this retrospective cohort study, the researchers compared the incidence rates of HZ between persons with and without COPD in the United States. Data for the study was obtained from an insurance database from January 2013 to December 2018.

A total of 1,61,970 participants with a diagnosis of COPD were categorized as $COPD^+$, while 9,643,522 participants without COPD diagnosis were grouped as $COPD^-$. Those with a history of HZ, prior HZ vaccination, postherpetic neuralgia (PHN), or HZ ophthalmicus were excluded from the study. Participants with COPD tended to be older in age, have more comorbid conditions and also used steroids more frequently than those without COPD. The incidence rate of herpes zoster was significantly higher in the $COPD^+$ cohort (13.0 per 1,000 person-years) compared to the $COPD^-$ cohort (2.3 per 1,000 person-years) with an adjusted incidence rate ratio (aIRR) of 2.77. COPD patients had a 5.7-fold higher incidence rate of HZ compared to those without COPD, even after adjustment.

The unadjusted incidence rate of PHN was 1.7 times higher in the $COPD^+/HZ^+$ group (64.8 per 1,000 person-years) compared to the $COPD^-/HZ^+$ cohort (37.1 per 1,000 person-years). However, after adjustment, this association was not statistically significant with aIRR of 1.07. The incidence rates of HZ and PHN increased with age across the cohorts. After adjusting for potential confounders, adults with COPD were found to have a 2.8-fold increased risk of developing HZ compared to those without COPD. These findings underscore the need for greater awareness about the risk of HZ, which is a very painful condition, in COPD patients. They also establish the importance of proactive targeted prevention strategies, including Shingles vaccination for those at higher risk.

Reference

1. Thompson-Leduc P, et al. Chronic obstructive pulmonary disease is associated with an increased risk of herpes zoster: a retrospective United States claims database analysis. Clin Respir J. 2022(12):826-34.

Central Obesity and Risk for Pelvic Organ Prolapse

Women with central obesity are at a higher risk of incident pelvic organ prolapse (POP). This risk is particularly pronounced in those younger than 60 years of age or do not have a history of hysterectomy. These findings were published online October 24, 2024, in the journal *Obstetrics & Gynecology*[1].

This prospective study was conducted to ascertain the association between central and general obesity and the risk of incident POP. A total of 2,51,143 participants, aged 39 to 71 years, without a history of POP from the UK Biobank were enrolled for the study between 2006 and 2010. Baseline data for waist/height ratio and body mass index (BMI). Central obesity was defined as waist/height ratio ≥0.5. Nearly 61% were postmenopausal and 17% had undergone hysterectomy prior to their enrollment for the present study.

Results showed 9,781 cases of POP over the median follow-up duration of 13.8 years. The risk of POP was increased by 48% among participants with central obesity, independent of BMI, with a hazard ratio (HR) of 1.48. Approximately 21.7% of all POP cases were attributable to central obesity.

The risk was 23% higher among women with overweight without central obesity (BMI 25-29.9 and waist/height ratio <0.5) with HR of 1.23. This accounted for 2.0% of all POP cases that were identified in the study. The association between risk of POP and central obesity was stronger among subjects younger than 60 years (vs. ≥60 years) (57% vs. 39%) and those without a history of hysterectomy (54% vs. 27%).

These findings therefore suggest that central obesity and overweight without central obesity are risk factors for POP. Combining waist-to-height ratio with BMI provides a more accurate assessment of risk for POP compared with using either alone. Higher waist/height ratio among women with the same BMI face a greater risk of POP than those with a normal ratio.

Reference

1. Si K, et al. Association of central and general obesity measures with pelvic organ prolapse. Obstet Gynecol. 2025;145(1):108-14.

■■■■

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Lighter Side of Medicine

HUMOR

WHAT IF I HAVE A BATH?

Mum: If you wash your face, Sammy, you can have one slice of chocolate cake. But if you wash your neck, too, you can have two slices.

Sammy: What if I have a bath?

DREAM OF A NECKLACE

After she woke up, a woman told her husband, "I just dreamed that you gave me a pearl necklace for our anniversary. What do you think it means?"

"You'll know tonight." he said.

That evening, the man came home with a small package and gave it to his wife.

Delighted, she opened it to find a book entitled "The Meaning of Dreams."

ABSENT-MINDED PROFESSOR

One of the world's greatest scientists was also recognized as the original absent-minded professor. One day, on board a train, he was unable to find his ticket. The conductor said, "Take it easy. You'll find it."

When the conductor returned, the professor still couldn't find the ticket. The conductor, recognizing the famous scientist, said, "I'm sure you bought a ticket. Forget about it."

"You're very kind," the professor said, "but I must find it, otherwise I won't know where to get off."

A TEXAS MILLIONAIRE

A Texas millionaire had fallen ill. The doctors consulted did not seem to understand what ailed him. The millionaire let it be known that any doctor who could heal him could have whatever he desired.

A country doctor was finally able to cure him, and as the doctor was leaving after a week's stay, the Texan said, "Doc! I am a man of my word. You name it, and if it is humanly possible I'll get it for you."

"Well," said the doctor, "I love to play golf, so if I could have a matching set of golf clubs, that would be fine." With that the physician left.

The doctor didn't hear from the Texan millionaire for some months. Then, one day, he got a phone call from the millionaire.

"Doc, I bet you thought that I had gone back on my word. I have your matching set of golf clubs. The reason it took so long is that two of them didn't have swimming pools, and I didn't think they were good enough for ya. So, I had pools installed and they're all ready for you now!"

DAUGHTER IN COLLEGE

Did you hear about the Banker who was recently arrested for embezzling $100,000 to pay for his daughter's college education?

As the Policeman, who also had a daughter in college, was leading him away in handcuffs, he said to the banker, "I have just one question for you. Where were you going to get the rest of the money?"

Dr. Good and Dr. Bad

SITUATION: A type 2 diabetic patient wanted to know his risk of heart failure.

LESSON: Only NT-proBNP strongly and consistently improved the prediction of heart failure in patients with T2DM beyond a wide range of clinical risk factors and biomarkers.

Diabetes Care. 2017;40(9):1203-9.

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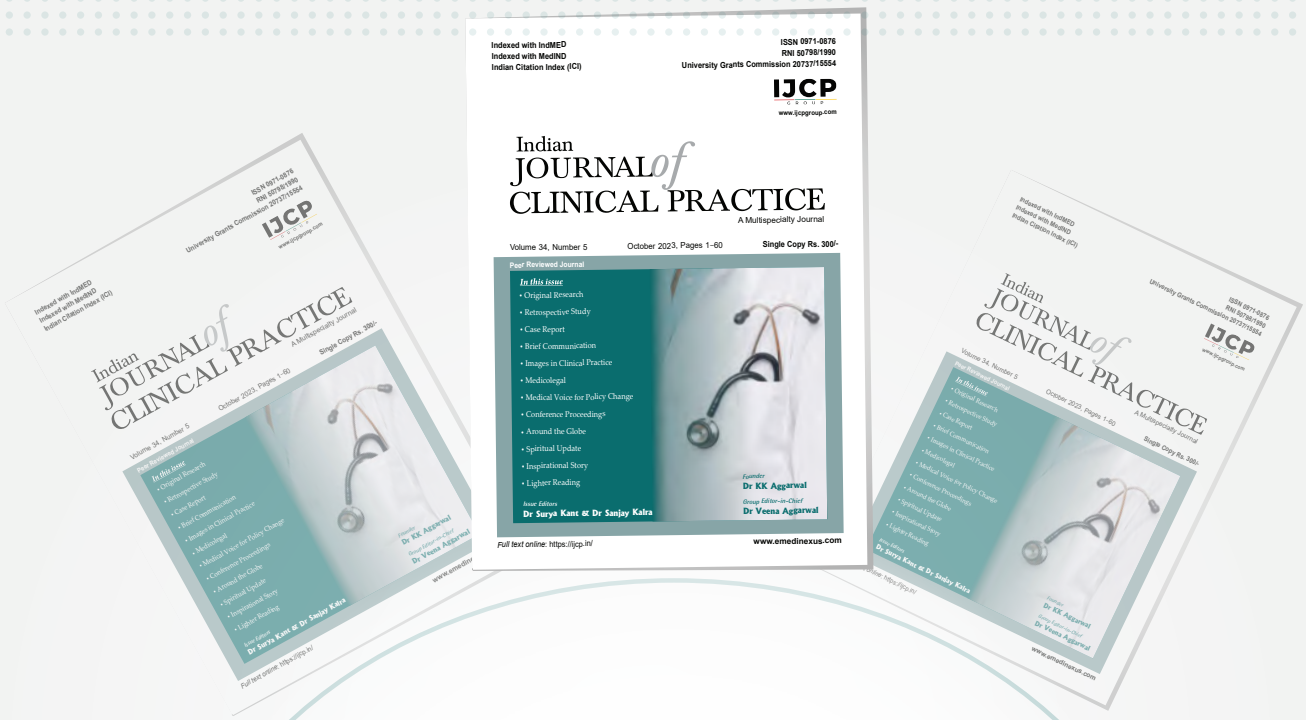

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- Method of allocating the subjects into different groups.
- Statistical methods used for presentation and analysis of data i.e., in terms of mean and standard deviation values or percentages and statistical tests such as Student's 't' test, Chi-square test and analysis of variance or non-parametric tests and multivariate techniques.
- Confidence intervals for the measurements should be provided wherever appropriate.

Results

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Discussion

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References

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Examples of common forms of references are:

Articles

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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Tables

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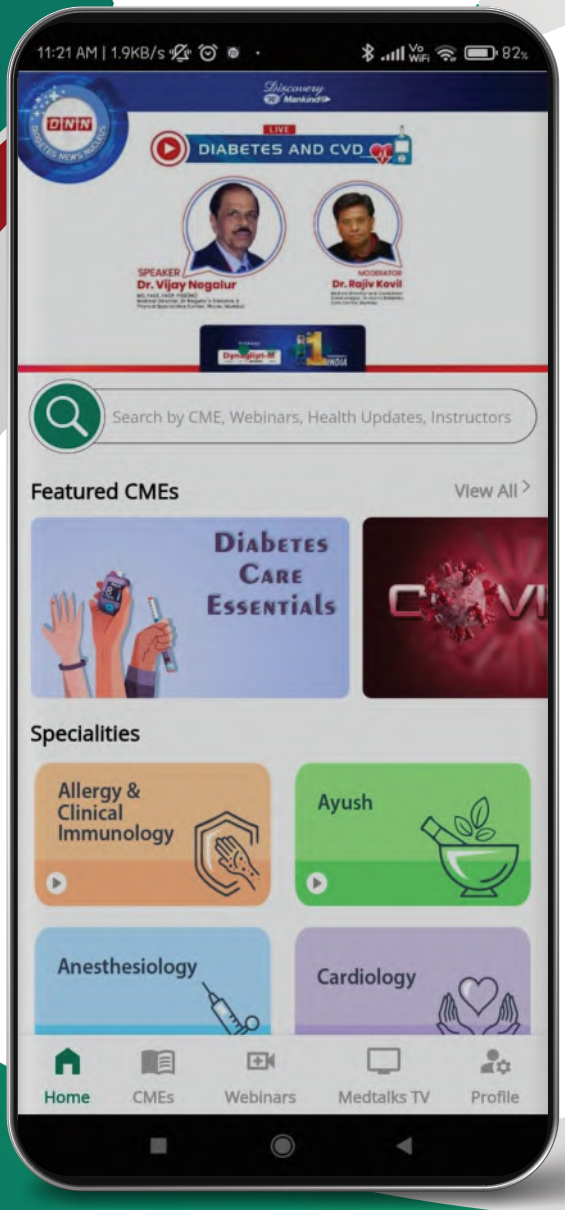

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