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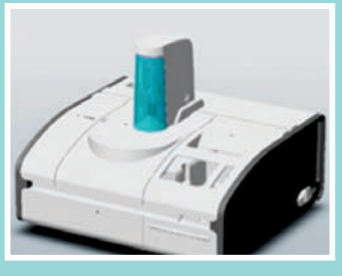

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Indian Journal of Clinical Practice, Vol. 31, No. 9, February 2021

Dr KK Aggarwal
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CMAAO Coronavirus Facts and Myth Buster: GI COVID

COVID-19: AFFINITY FOR THE DIGESTIVE SYSTEM

- February: Presence of gastrointestinal (GI) symptoms was reported in the first case of coronavirus disease 2019 (COVID-19) in the US.
- In the early days, the focus was on respiratory symptoms and transmission; however, researchers from China soon identified the GI/fecal/oral route as another avenue of spread for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.
- The oral route acts as a point of entry into the body and the digestive tract is a primary organ system for the multiplication, replication and potential spread of the virus, as per Brennan Spiegel, MD, of Cedars-Sinai Medical Center in Los Angeles.
- Experts quickly cautioned that extrapulmonary complications in the GI tract might be more common than previously thought and should not be missed in the differential diagnosis.
- Also GI symptoms, which appeared to affect 5-15% of patients, often persisted after the acute phase of the infection and sometimes pointed to poorer outcomes.
- Besides the February report, US and Chinese researchers suggested that digestive symptoms were a possible hallmark of COVID-19 infection in some patients. Doctors were advised to assess all patients with GI complaints for the virus.
- In March, increasing evidence of such symptoms in about 50% of patients prompted several US GI societies to issue a message on clinical precautions for providers of endoscopy and other gastroenterology care.
- Around the same time, a Chinese study showed that in a subgroup of COVID-19 patients with mild disease, digestive problems, such as nausea and diarrhea, might be the only symptoms, with no sign of fever or respiratory symptoms and should, therefore, be part of the differential diagnosis.
- Early May: Clinicians from New York revealed that 22% of hospital-assessed COVID-19 patients had diarrhea, 7% had abdominal pain, 16% had nausea and 9% had vomiting. Overall, 33% of patients had at least one GI manifestation, and 62% of patients had biochemical evidence of liver injury.
- Chinese researchers showed that 50.5% of COVID-19 patients presenting at hospitals had at least one digestive tract symptom and among nearly half of these patients, a digestive problem was the chief complaint. GI involvement was associated with longer hospital stay and worse outcomes - only

34.3% of those with digestive symptoms recovered while 60% of patients without digestive symptoms were discharged as recovered.

- By July, Italian physicians reported that hospitalized patients had lingering symptoms, including troublesome GI manifestations, for up to 2 months after recovering from the acute phase.
- A California study linked the use of a proton pump inhibitor (PPI) to a heightened risk of COVID-19 positivity.
- August: Research revealed that the virus can present as acute idiopathic pancreatitis and Black and Hispanic patients with existing pancreatitis were more vulnerable to COVID-19.
- Fall: Chicago clinicians presenting at the 2020 American College of Gastroenterology (ACG) virtual meeting noted that GI symptoms at initial presentation had an independent association with poor prognosis. **Diarrhea at presentation was associated with more severe disease and poor prognosis, suggested a review and meta-analysis also presented at the meeting.**
- North American Alliance for the Study of Digestive Manifestation of COVID-19 suggested that while severe GI complications admitted to the ICU were uncommon (5.1%), they were tied to a death rate of 55.6%. While the study demonstrated a low incidence of intestinal ischemia, investigators cautioned that COVID-19 is a hypercoagulable disorder, associated with a higher incidence of venous thromboembolism. **It can potentially infect the endothelial cells of different vascular beds in the heart, small bowel and lungs. Therefore, endotheliitis caused by COVID-19 can result in microthrombus formation and organ ischemia.**
- As per Brett Williams, MD, of Chicago's Rush University Medical Center, "We know this virus has a propensity to cause endotheliitis, which can obviously involve any organ. Patients with GI symptoms quite possibly have direct viral invasion of the GI mucosa, liver and pancreas, though in sepsis-type syndromes, **it's difficult to know how much the inciting pathogen, hypoperfusion and inflammation each contribute to pathology in any one organ system.**" He said that at his center, raised lipase levels in COVID-19 patients were relatively common, seen in 16.8% of those patients checked, and elevated lipase levels had a robust association with ICU admission and intubation. He added that receptors for the virus appear to be there in the pancreas, as well as in mature enterocytes.
- December: A hospital study from New York revealed that 3% of COVID-19 inpatients had GI bleeding, which was associated with higher mortality.
- Most implicated in GI involvement are angiotensin-converting enzyme 2 (ACE2) receptors which are in abundance in the intestines as well as the stomach and liver.
- Respiratory virus sheds into saliva from the shared upper airways and the salivary glands. Once swallowed, the viral-laden saliva passes through the acid layer making use of the ACE2 receptors to enter epithelial cells lining the intestine, where it undergoes replication. The gastric acid can inactivate most viruses. However, if the virus hits before the first meal of the day when the acid levels are low, or if one is taking a PPI or gets a large inoculum of virus, enough of it can get through to make it past.
- The long-haul effects of COVID-19, such as chronic diarrhea and nausea, can intensify pre-existing GI conditions, including irritable bowel syndrome (IBS) and other chronic problems.
- The virus can potentially disrupt the gut microbiome and exacerbate the mental anguish that these patients already feel.
- The virus may also trigger new-onset post-viral IBS.

(*Medpage Today Excerpts*)

With input from Dr Monica Vasudev

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Indian Journal of Clinical Practice, Vol. 31, No. 9, February 2021

Acute Seizure in Hyponatremia

AMIT KUMAR*, VN JHA†

ABSTRACT

Introduction: Acute and severe electrolyte imbalances can manifest with seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia and hypomagnesemia. An accurate and prompt diagnosis should be established for successful management of seizures, as rapid identification and correction of the underlying electrolyte disturbance (rather than an antiepileptic treatment) are of crucial importance in the control of seizures and prevention of permanent brain damage. **Aims and objectives:** To study the incidence of seizure in hyponatremia. **Material and methods:** Two hundred patients were chosen from indoor settings and studied for seizure among hyponatremic patients. **Results and Conclusion:** Seizure generally occurred in severe hyponatremia with the incidence being 4%.

Keywords: EEG, electrolyte, epilepsy, seizures, hyponatremia

Acute and/or severe electrolyte imbalances can manifest with rapidly progressive neurologic symptoms or seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia and hypomagnesemia. Epidemiological data show that electrolyte disturbances (especially hyponatremia) represent a frequent cause of acute symptomatic nonfebrile seizures in patients of any age. Electrolyte disturbances may cause diffuse brain dysfunction that can be assessed by means of EEG recording. In general, the most prominent feature of the EEG record in metabolic encephalopathies is a slowing of the normal background frequency. EEG evolution generally correlates well with the severity of encephalopathy; more specifically, the degree and severity of EEG abnormalities correlate with the rate of change of electrolyte balance rather than with the absolute level of a specific electrolyte or metabolite.

Hyponatremia is defined as a serum sodium level of <135 mEq/L and is considered severe when the serum level is <125 mEq/L.

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The major clinical complications from acute hyponatremia are brain cell swelling and herniation with neurologic symptoms being evident when hyponatremia approaches 120 mEq/L. The risk of cerebral edema and neurologic manifestations is minimized if the decline in serum sodium occurs slowly and gradually (≥48 h), even in case of a marked absolute reduction of serum sodium values. Conversely, in case of a rapid decrease in serum sodium (acute hyponatremia), cerebral edema with neurologic symptoms are likely to occur.

The neurological symptoms of hyponatremia therefore go in parallel with the severity of cerebral edema, and are less frequently induced by chronic than by acute hyponatremia: approximately half of the patients with chronic hyponatremia are asymptomatic, even with serum sodium concentration <125 mEq/L. In these patients, symptoms are rarely noted until the serum sodium is <120 mEq/L and are more frequently seen with values of ≤110 mEq/L.

Hyponatremia represents a frequent cause of epileptic seizures, as shown in a prospective observational multicenter study where acute epileptic seizures and focal neurological deficits were identified in 5% of patients each, with severe (<125 mEq/L) hyponatremia.

MATERIAL AND METHODS

A total of 200 indoor patients were chosen and routine blood tests were done and serum electrolytes were assessed, especially for serum sodium.

Table 1. Patients with Hyponatremia

Total patients with hyponatremia	Mild hyponatremia (Na 130-134 mEq/L)	Moderate hyponatremia (Na 125-129 mEq/L)	Severe hyponatremia (Na <125 mEq/L)
50	35	5	10

Table 2. Patients with Seizure and Altered Sensorium

Hyponatremic	With seizure	With altered sensorium
50	2 (4%)	7 (14%)

RESULTS

Fifty patients were found to have serum sodium <135 mEq/L (Table 1). Among 50 hyponatremic patients, 10 had sodium level <125 mEq/L, and among these, 2 patients developed seizure and 7 had altered sensorium (Table 2). Seizure did not occur in patients with serum sodium >125 mEq/L.

DISCUSSION AND CONCLUSION

Hyponatremia is a frequent cause of epileptic seizures. In our study, the incidence of seizure disorder in patients with hyponatremia was found to be 4%.

The neurological symptoms in these patients are rarely seen until the serum sodium is <120 mEq/L. Particularly, the children are at high risk of developing symptomatic hyponatremia, because of their larger brain-to-skull size ratio. Severe and rapidly evolving hyponatremia may cause seizures, which are usually generalized tonic-clonic, and generally occur if the plasma sodium concentration rapidly declines to <115 mEq/L.

Early identification and correction of these disturbances are necessary to control seizures and prevent permanent brain damage, as antiepileptic drugs (AED) alone are generally ineffective if the electrolyte disorder persists. In fact, treatment of seizures secondary to electrolyte imbalances is largely driven by the underlying cause of the disturbance, and in most cases, administration of AED is not necessary as long as the underlying disturbance is corrected.

We physicians should be vigilant to recognize and treat acute electrolyte imbalance in the best possible way so that irreversible brain damage can be prevented and patient recovers completely.

SUGGESTED READING

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Generic and Branded Formulations: A Comparative Research on Quality Parameters

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ABSTRACT

When a pharmaceutical company first markets a new drug, it is usually under a patent. All the manufacturers pay patent royalty to the patentee company to get share of the sole right of manufacturing the innovated drug during its patent period. After the patent period is completed, drug manufacturers do not require paying royalty thereafter. Patent royalty is the major stake of the price. Even after completion of the patent period, the prices of some branded medicines are still high. Generic medicines contain the same active ingredient with same quantity whose patent is expired, and hence cost cheaper than the branded medicine. As the gap in prices of generic and branded medicine is high, false notions like "generics do not comply to the quality standards" is circulating among the public. To eradicate that notion, an attempt was made taking three regular usage drugs – telmisartan, glimepiride and atorvastatin – to compare their quality standards both in branded and generic formulations. The outcome has proved that generics are no way inferior to the branded formulations. Moreover, generic formulations proved to be quite close to the stipulated standards in all the three drugs. Wide publicity is required about generic drugs to swipe off false notions.

Keywords: Generic, branded, patent, royalty, comparative, quality parameters, telmisartan, glimepiride, atorvastatin, physical evaluation, thickness, hardness, friability, disintegration test, dissolution test, absorption maxima

Generic medicines contain the same active ingredient in the same quantity as a branded medicine. Generic medicines, thus tend to have the same impact on the body when it comes to curing a disease as the brand-named medicines.

Generic medicines are sold using a different name and may have different inactive ingredients compared with the branded ones. Inactive ingredients are the ones that give the product its taste, shape, texture, smell, etc., but do not have a role in relieving the health conditions. Although the use of generic medicines is becoming more widely accepted by doctors and consumers, many still don't trust generic medicines. Further, use of generic medication still remains a controversial issue amongst doctors.

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The generic pharmaceutical industry is growing, and these medicines will possibly become more common in the future. There is an urgent need for enhanced education about generic medicines and the similarities and differences between generic and brand-name medicines. Enhanced knowledge is also needed on the testing that is conducted to ensure that generic medicines are safe and have the same effect on the body as the branded medicine, which is known as therapeutic bioequivalence.

BRANDED MEDICINE

A branded medicine is the original product developed by a pharmaceutical company. When a new medicine is developed, it is subjected to rigorous tests and evaluations in order to ensure that it can effectively cure the condition it claims to treat and is safe for human use. Pharmaceutical companies invest to develop a new medicine, hence receive the sole right to manufacture and distribute the medicine for a certain period of time.

When a pharmaceutical company attains sole rights of manufacture and distribution, the medicine is said to have a patent on it. A patent refers to a technical description of the drug and what it is used for.

For a certain amount of time after the patent is granted, no one else can produce a drug which is the same as the patented drug. This is why branded medicines are well known and the most trusted type of that particular medicine.

GENERIC MEDICINE

A generic medicine is one that has the same chemical substance as the drug that was originally developed, patented and innovated. Generic drugs are allowed for sale after the expiry of the patent of the original drugs. The active chemical substance being the same, generics are considered to have a medical profile equivalent in performance. The generic drug has the same active pharmaceutical ingredient (API) as the original drug; however, the difference may lie in the manufacturing process, formulation, excipients, color, taste, packaging, etc.

A generic medicine is a copy of the branded product. Once the patent for the original product expires, the pharmaceutical company that developed the medicine no longer enjoys the exclusive right to produce and distribute the medicine. Other pharmaceutical companies can now develop their own version of the medicine. The type and quantity of the active ingredient in the generic product remains the same, but the inactive ingredients differ. The generic medicine is sold under a different brand name and may look different to the original.

GENERIC DRUG RESEARCH

When an application is approved, the generic drug is added to the Food and Drug Administration (FDA) list of Approved Drug Products with Therapeutic Equivalence Evaluations. The FDA elucidates the list to show equivalence between the reference-listed drug and the generic. In order to start selling a drug once the patent on innovator drug expires, a generic company is required to file its Abbreviated New Drug Application (ANDA) before the patent expires. However, this puts the generic company at risk of being sued for patent infringement; filing the ANDA is regarded as constructive infringement of the patent.

INDIAN SCENARIO

The Indian government began encouraging more drug manufacturing by Indian companies in the early 1960s and with the Patents Act in 1970. The Patents Act removed composition patents for foods and drugs; the process patents were kept, but were shortened to a period of 5-7 years. The resulting lack of patent protection created a niche in both the Indian and global markets that Indian companies filled by reverse engineering novel processes for manufacturing low-cost drugs. The code of ethics issued by the Medical Council of India (MCI) in 2002 called physicians to prescribe drugs by their generic names only. India is a leading country in the world's generic drugs market.

AIMS AND OBJECTIVES

The aim of the study is to compare generic and branded formulations of an antihypertensive drug, antidiabetic drug and an antihyperlipidemic drug. The objective of the study is to elucidate a report on comparative study of generic and branded formulations of telmisartan, glimepiride and atorvastatin and to deliberate the reality on standards of generic formulations.

EXPERIMENTAL

Three drugs were selected for comparison of generic and branded formulations. As the drugs are out of patent period, generic formulations are also available.

MATERIAL AND METHODS

The selected drugs comprise regularly used antihypertensives, antidiabetics and antihyperlipidemic drugs. The selected trade names are fast moving formulations in the present market. Among the available drugs, three drugs were selected for which both branded and generic formulations were available. Selectively an antihypertensive, an antidiabetic and an antihypercholesterolemia drug were selected (Tables 1 and 2).

Telmisartan Tablets IP

The angiotensin receptor blockers (ARBs), or AT-I receptor antagonists, are antihypertensive drugs acting by blocking the effects of the hormone angiotensin-II in the body, thus reducing blood pressure. Their structure is similar to AT-II and bind to AT-II receptors as inhibitors.

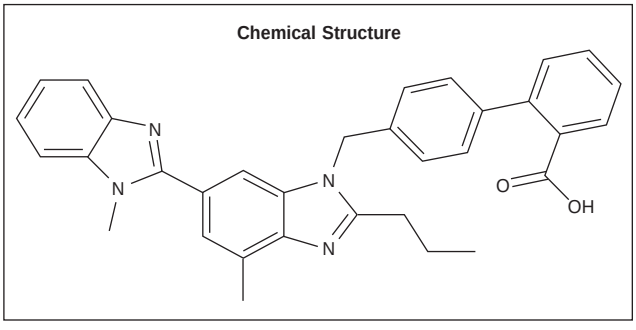


Table 1. Drugs Selected for Research

Drug name and dose	Category
Telmisartan IP 40 mg	Antihypertensive drug
Glimepiride IP 1 mg	Antidiabetic drug
Atorvastatin calcium IP 10 mg	Antihyperlipidemic drug

Table 2. Drugs Selected (*Research Done During February 2019*)

Pure drug	Branded Formulation				Generic Formulation			
	Batch Number	Mfg. Date	Expiry Date	Company Name	Batch Number	Mfg. Date	Expiry Date	Company Name
Telmisartan (40 mg)	Confidential	08/2018	07/2020	The name of the company is kept confidential to protect the integrity	Confidential	07/2018	06/2020	The name of the company is kept confidential to protect the integrity
Glimepiride (1 mg)	Confidential	03/2018	2/2020	The name of the company is kept confidential to protect the integrity	Confidential	2/2018	01/2020	The name of the company is kept confidential to protect the integrity
Atorvastatin (10 mg)	Confidential	01/2018	05/2020	The name of the company is kept confidential to protect the integrity	Confidential	12/2017	11/2019	The name of the company is kept confidential to protect the integrity

Medical uses

Telmisartan is used to treat high blood pressure, heart failure and diabetic kidney disease.

Contraindications

Telmisartan is contraindicated during pregnancy. Similar to other drugs that affect the renin-angiotensin system (RAS), telmisartan can cause birth defects, stillbirths and neonatal deaths. It is not known if the drug passes into breast milk. It is contraindicated in bilateral renal artery stenosis.

Side effects

Side effects include tachycardia and bradycardia, hypotension, edema (swelling of arms, legs, lips, tongue or throat, the latter leading to breathing problems) and allergic reactions.

Interactions

Due to its mechanism of action, telmisartan increases blood potassium levels. Combination with potassium preparations or potassium-sparing diuretics could cause hyperkalemia. Combination with nonsteroidal anti-inflammatory drugs (NSAIDs), particularly in patients with impaired kidney function, can cause (usually reversible) kidney failure.

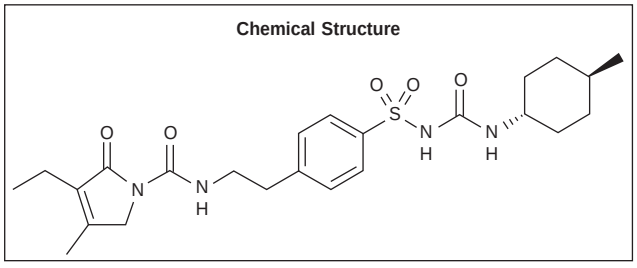
Glimepiride Tablets IP

Glimepiride, a second-generation sulfonylurea, is used to treat type 2 diabetes mellitus. Its use is recommended with diet and exercise. It is an oral drug and takes up to 3 hours for maximum effect and the effect lasts for about a day.

Common side effects include headache, nausea and dizziness. Serious side effects may include low blood

sugar. Use in pregnancy and breastfeeding is not recommended. The drug acts by increasing the amount of insulin released from the pancreas.

Glimepiride was patented in 1979 and approved for medical use in 1995. It is available as a generic medication.



Medical uses

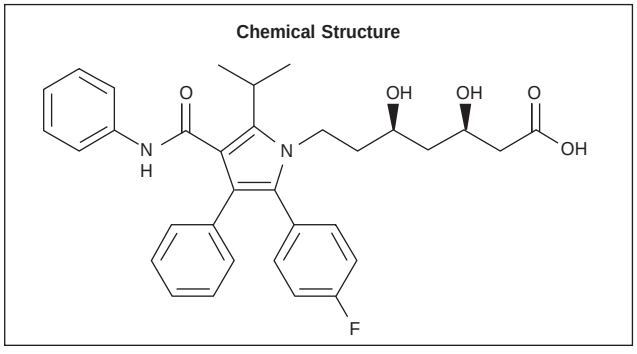
The drug is used to treat type 2 diabetes mellitus by increasing insulin secretion by the pancreas. However, it requires adequate insulin synthesis as a prerequisite to treat appropriately. It is not used for type 1 diabetes.

Atorvastatin Calcium Tablets IP

Bruce Roth, in 1982, developed an experimental compound that was named CI 981, and later came to be known as atorvastatin. It was first made in August 1985. Bruce Roth, Roger Newton and Ronald Cresswell in 1985, convinced their company to move the compound into expensive clinical trials. Early results comparing atorvastatin with simvastatin showed that atorvastatin appeared more potent and had fewer side effects.

In 1994, the findings published in *The Lancet* demonstrated the efficacy of statins in lowering cholesterol, thus proving for the first time that a statin reduced low-density lipoprotein (LDL) cholesterol and also led to a sharp decline in fatal heart attacks among individuals with heart disease.

By 2003, atorvastatin had become the best selling pharmaceutical in the United States. From 1996 to 2012, atorvastatin became the world's best-selling medication of all time.



Medical uses

In dyslipidemia

- Hypercholesterolemia (heterozygous familial, non-familial) and mixed dyslipidemia (Fredrickson types IIa and IIb) to reduce total cholesterol, LDL cholesterol, apo-B, triglyceride levels and C-reactive protein (CRP) as well as increase high-density lipoprotein (HDL) levels.
- Heterozygous familial hypercholesterolemia in pediatric population.
- Homozygous familial hypercholesterolemia.
- Hypertriglyceridemia (Fredrickson type IV).
- Primary dysbetalipoproteinemia (Fredrickson type III).
- Combined hyperlipidemia.

In cardiovascular disease

- Primary prevention of heart attack, stroke and need for revascularization procedures in individuals with risk factors, including age, smoking, high blood pressure, low HDL cholesterol and a family history of early heart disease, but who have not yet developed evidence of coronary artery disease (CAD).
- Secondary prevention of myocardial infarction, stroke, unstable angina and revascularization in people with established CAD.
- Myocardial infarction and stroke prevention in people with type 2 diabetes.

  High-dose statin therapy appears to play a plaque-stabilizing role in those with acute coronary syndrome and thrombotic stroke.

In kidney disease

Statins, including atorvastatin, have a small, but significant beneficial effect on preventing the loss of kidney function and on reducing loss of protein in urine in people with cardiovascular disease.

Preoperative treatment with statins, including atorvastatin, does not prevent acute kidney injury in persons having cardiac surgery.

METHODOLOGY FOR COMPARATIVE STUDY

The selected generic and branded formulations of telmisartan, glimepiride and atorvastatin were compared for their quality standards basing on 8 quality control parameters.

1. Physical evaluation
2. Thickness

3. Hardness
4. Friability
5. Assay
6. Disintegration test
7. Dissolution test
8. Absorption maxima.

Depending upon the results obtained, quality of the formulation can be defined.

Physical Evaluation

- **Color:** Color of the tablet was recorded.
- **Odor:** Odor of the tablet was recorded.

Thickness

Tablet thickness is a key quality control test. Very thick tablet can affect packaging either in blister or a plastic container. Tablet thickness is determined by the measurement of the uniform diameter of the tablet.

Hardness

The test measures a property of the tablet called CRUSHING STRENGTH which is defined as the compressional force applied diametrically to a tablet that just fractures it. Hardness tester (Cobb's) is among the most favored measuring devices. This is manually used. Some hardness testers are motor driven.

Friability

The tablet may undergo a tumbling motion. Coating, packaging, transport may not be severe enough to break the tablet, but may abrade the small particle from tablet surface. Therefore, tablets are subjected to a uniform tumbling motion for a specified time and weight loss is assessed.

Assay

Thirty tablets are randomly selected; 10 of these are assayed individually. The tablets pass the test if 9 of the 10 tablets contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not have less than 75% and more than 125% of the labeled content. If these conditions are not fulfilled, remaining 20 tablets are assayed individually and none of them may fall outside of the 85-115% range.

Disintegration Test

The breakage of tablet into smaller fragments is called disintegration of tablet. The USP device uses 6 glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To assess disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 20°C such that the tablet is 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets is moved up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. Floating of the tablets is prevented by placing perforated plastic discs on each tablet. The tablet must disintegrate and all particles must pass through the 10 mesh screen in the stipulated time. If any residue remains, it must have a soft mass.

- Disintegration time: Uncoated tablet: 5-30 minutes.
- Coated tablet: 1-2 hours.

Dissolution Test

The release of drug from the tablet into solution per unit time under standardized condition is termed as the dissolution test.

Basket Type: A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft which is connected to a variable speed motor. The basket is immersed in a dissolution medium contained in a 1,000 mL flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37°C (±0.5) by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid is withdrawn at intervals to determine the amount of drug in solutions.

Absorption Maxima

In order to select analytical wavelength, 2.5 µg/mL of the selected drug is prepared by appropriate dilution of standard stock solution and subjected to scanning in the spectrum mode from 400 nm to 200 nm. From the scanned spectra, suitable Absorption maxima [Lambda Max] of the drug is selected for the analysis. The calibration curve is prepared in the concentration in the suitable range of 0.1-4 µg/mL at suitable wavelength (nm). By using the calibration curve, the concentration of the sample solution can be determined.

RESULTS AND DISCUSSION

Generic Telmisartan vs. Branded Telmisartan

Quality parameters of generic and branded formulations were compared (Table 3 and Figs. 1-5).

Table 3. Quality Parameters of Generic and Branded Formulations of Telmisartan

Parameters (with standard/ideal values in brackets)	**Generic**	**Branded**	**Inference**
Drug name	Telmisartan	Telmisartan	Same API
Trade name	Confidential	Confidential	Both have trade names
Company name	Company name is kept confidential	Company name is kept confidential	Produced by established pharma companies
Drug quantity (mg)	40 mg	40 mg	Same quantity
Physical evaluation			Similar appearance
Color	Cream	White	
Odor	None	None	
Thickness (mm) No defined standards	3.574 mm	2.832 mm	Generic is thicker than branded.
Hardness (4-10 kg/cm^2)	2.37	1.56	Both are <4 kg. Generic is closer than branded.
Friability (NMT 0.5-1% weight loss)	1.53%	0.62%	Weight loss is just above the standard for generic.
Assay (90-110% purity)	97.26%	97.24%	Purity is within the standards.
Disintegration test (15 min in water with 37°C)	4.38 min	9.59 min	Generic is fast disintegrated than branded.
Dissolution test (95-105% of drug release)	95.61%	82.37%	Dissolution is within the standards for generic and deviated for branded.
Determination of absorption maxima	299 nm	290 nm	Absorption maxima of both is close to each other.

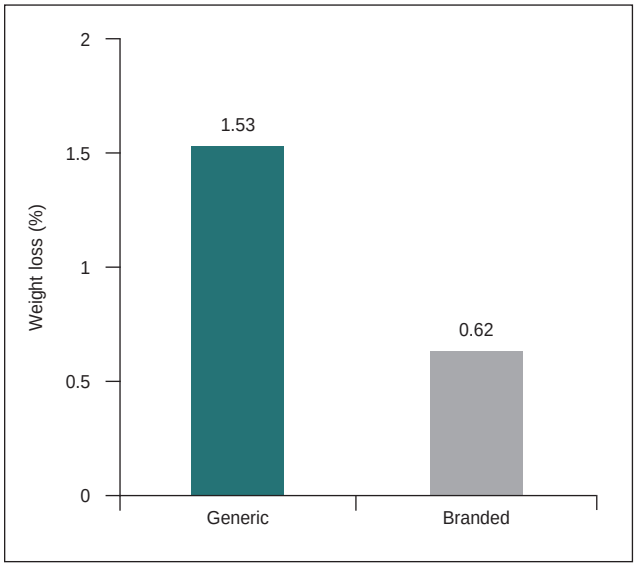


Figure 1. Telmisartan friability.

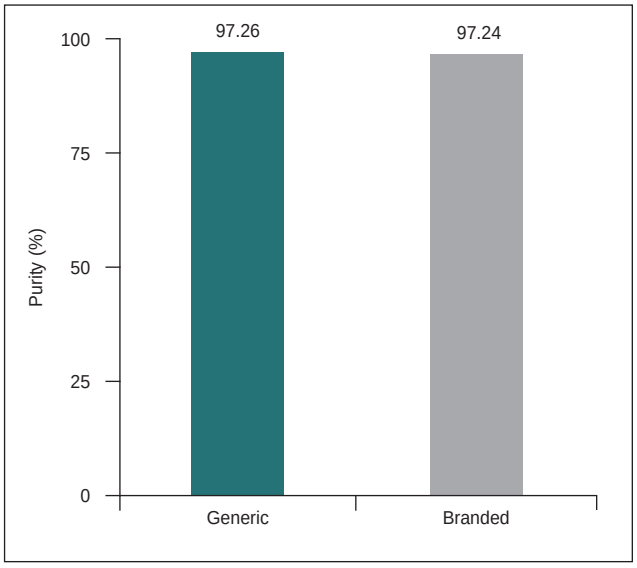


Figure 2. Telmisartan assay.

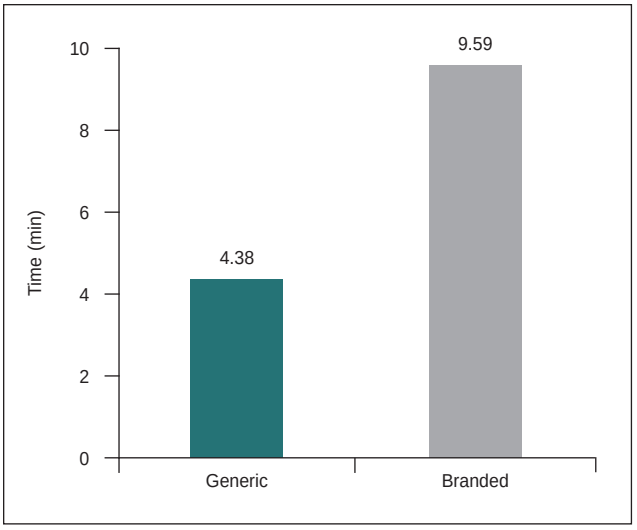


Figure 3. Telmisartan disintegration test.

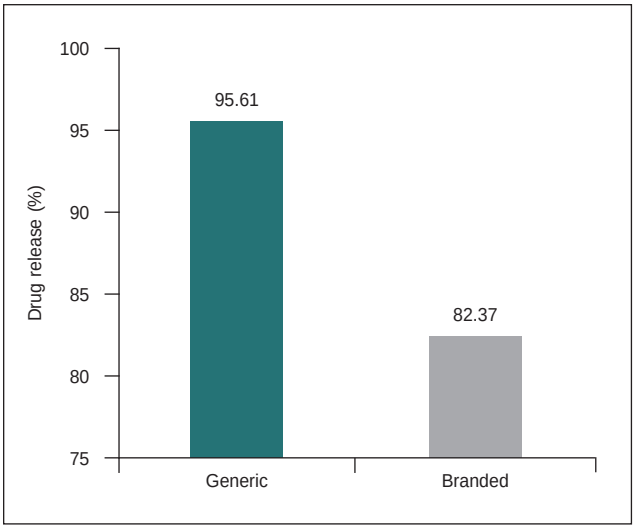


Figure 4. Telmisartan dissolution test.

Observations

- Active Pharmaceutical Ingredient (original drug) is same in both tablets.
- Both have trade names.
- Both are produced by established pharmaceutical companies.
- Both have same quantity and similar appearance.
- Generic tablet is thicker than branded one.
- Hardness of both is <4 kg/cm^2. Generic is closer to the standards.
- Weight loss in friability is beyond the standards for the generic.
- Purity is within the standards for the both.
- Generic is disintegrated faster than branded. Branded tablet has taken double the time compared to generic. However, both are within the standard limits.
- Dissolution is within the standards for generic and deviated for branded tablet. The percentage deviation in the drug release is around 12%.
- Absorption maxima of both are close to each other.

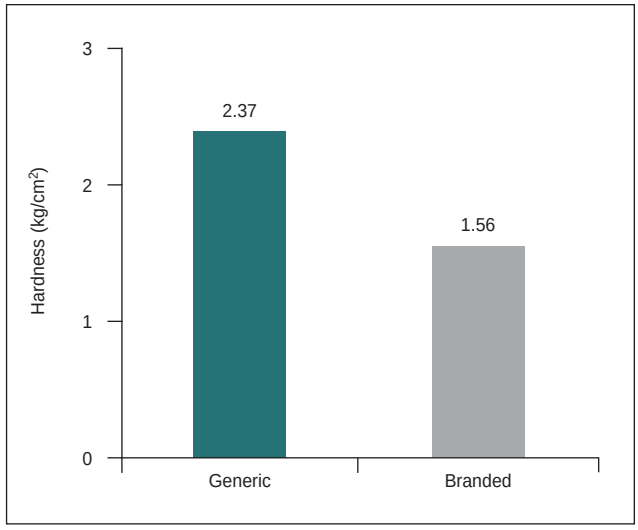


Figure 5. Telmisartan hardness.

Report

Hardness of both tablets did not meet the standards. However, generic tablet was closer to the standard than the branded tablet. During friability test, the loss of weight was beyond the standards for generic tablet. As far as purity is concerned, generic was little purer than the branded. Drug release in dissolution test was 12% deviated in branded, whereas generic tablet released the drug as per the limits of the standards. These observations collectively show that weight loss in friability was 0.5% more in generic but dissolution drug release was over 12% more than that of branded. Hence, generic is not inferior to the branded tablet.

Generic Glimepiride vs. Branded Glimepiride

Quality parameters of generic and branded formulations were compared (Table 4 and Figs. 6-9).

Observations

- API is same in both tablets.
- Both have trade names.
- Both are produced by established pharmaceutical companies.
- Both have same quantity and have similar appearance.

Table 4. Quality Parameters of Generic and Branded Formulations of Glimepiride

Parameters (with standard/ideal values in brackets)	**Generic**	**Branded**	**Inference**
Drug name	Glimepiride	Glimepiride	Same API
Trade name	Confidential	Confidential	Both have trade names
Company name	Company name is kept confidential	Company name is kept confidential	Produced by established pharma companies
Drug quantity (mg)	1 mg	1 mg	Same quantity
Physical evaluation			Similar appearance
Color	White molten starch	White starch	
Odor	None	None	
Thickness (mm) No defined standards	3.384 mm	2.081 mm	Generic tablet is thicker.
Hardness (4-10 kg/cm^2)	2.12	1.83	Both are <4 kg. Generic is closer than branded.
Friability (NMT 0.5-1% weight loss)	1.13%	1.25%	Weight loss is just above the standard for both.
Assay (90-110% purity)	98.66%	98.63%	Purity is within the standards.
Disintegration test (15 min in water with 37°C)	0.13 min	3.29 min	Generic is fast disintegrated than branded.
Dissolution test (95-105% of drug release)	96.13%	96.75%	Dissolution is within the standards.
Determination of absorption maxima	211 nm	208 nm	Absorption maxima of both is close to each other.

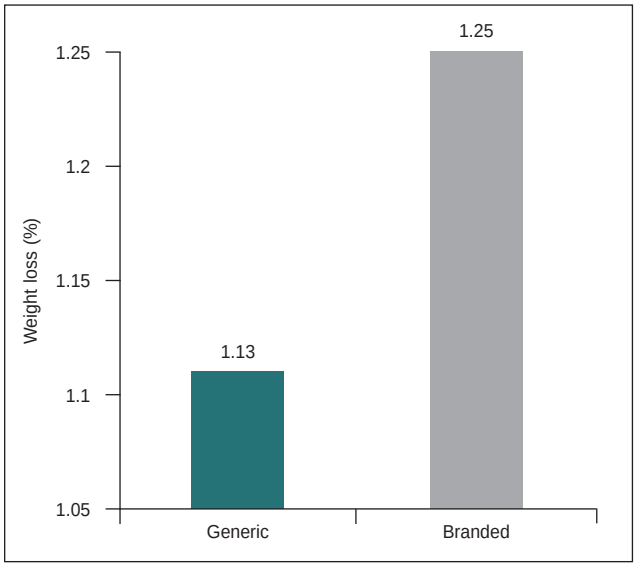


Figure 6. Glimepiride friability.

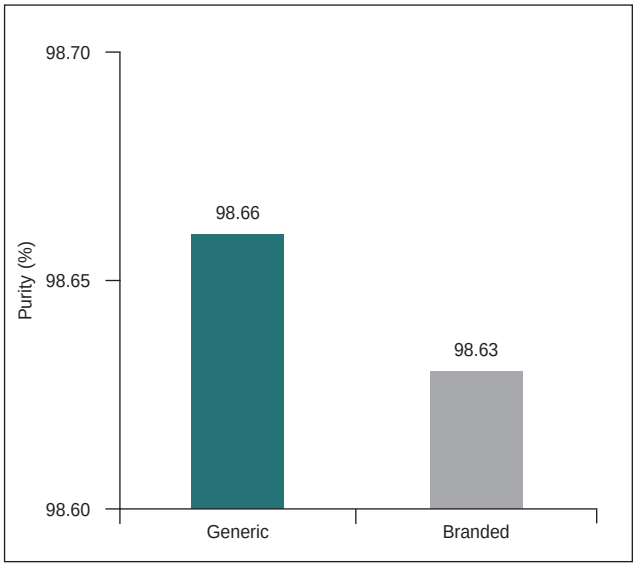


Figure 7. Glimepiride assay.

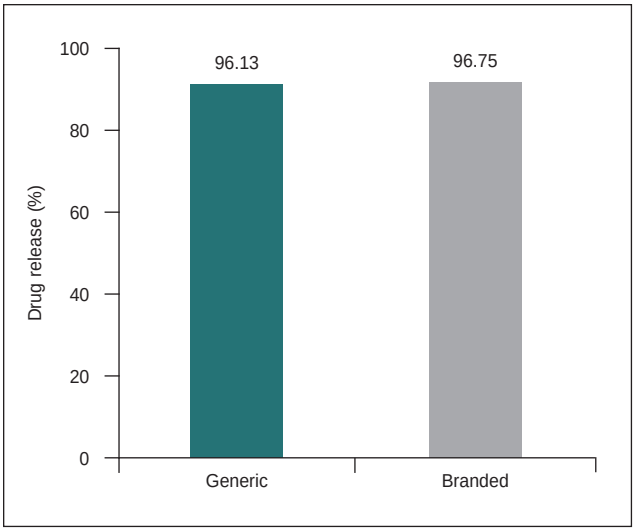


Figure 8. Glimepiride dissolution test.

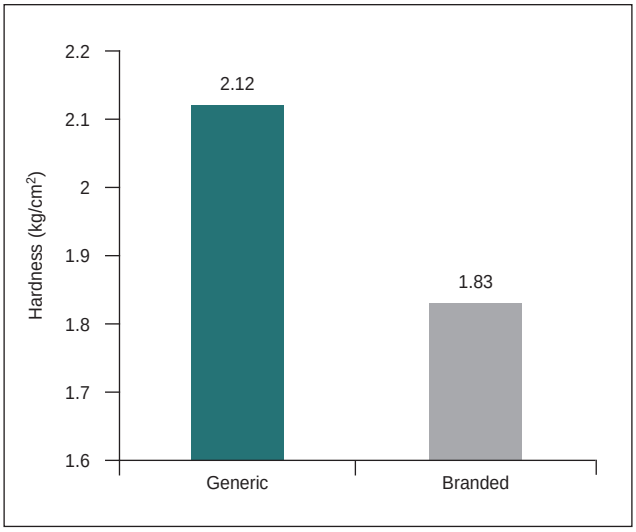


Figure 9. Glimepiride hardness.

- Generic tablet is thicker. However, thickness has no implication on their quality.
- Hardness of both is <4 kg/cm^2. Among the both, generic is closer to the standard than branded.
- Weight loss in friability is just above the standards for the both; generic is closer to the standards.
- Percentage purity is within the standards. Generic is purer than the branded tablet.
- Generic is disintegrated fast; however, both are within the standards.
- Dissolution is within the standards for both. Branded has released approximately 1% more drug within the stipulated time.
- Absorption maxima of both are close to each other.

Report

Hardness of both tablets did not meet the standards. However, generic tablet was closer to the standard than the branded tablet. During friability test, the loss of weight was just above the standards for the both. As far as purity is concerned, generic was purer than the branded. Drug release in dissolution test was less in generic than that in branded tablet. These observations collectively show that generic was not inferior to the branded tablet. In spite of these standards, the generic tablet is economical and 50% cheaper than the branded tablet.

Generic Atorvastatin vs. Branded Atorvastatin

Quality parameters of generic and branded formulations were compared (Table 5 and Figs. 10-15).

Observations

- API is same in both tablets.
- Both have trade names.
- Both are produced by established pharmaceutical companies.
- Both have same quantity.
- Both have similar appearance.
- Both tablets are of almost same thickness.
- Hardness of both is <4 kg/cm^2. Branded is closer to the standard than generic.
- Weight loss in friability is within the standards for generic and deviated for branded.
- Percentage purity is within the standards.
- Disintegration for both is within standards.
- Dissolution is within the standards for generic and beyond the standards for branded.
- Absorption maxima of both are close to each other.

Report

Hardness of both tablets did not meet the standards. However, branded tablet is closer to the standard than the generic tablet. During friability test, the loss of weight was more in branded tablet. Drug release in dissolution test was less in branded than that of generic tablet. These observations collectively show that generic was nearly conforming to the quality control standards equally with branded tablet. In spite of these standards, the generic tablet is economical and 50% cheaper than the branded tablet.

Table 5. Quality Parameters of Generic and Branded Formulations of Atorvastatin

Parameters (with standard/ideal values in brackets)	**Generic**	**Branded**	**Inference**
Drug name	Atorvastatin	Atorvastatin	Same API
Trade name	Confidential	Confidential	Both have trade names
Company name	Company name is kept confidential	Company name is kept confidential	Produced by established pharma companies.
Drug quantity (mg)	10 mg	10 mg	Same quantity
Physical evaluation			Similar appearance
Color	White	White	
Odor	None	None	
Thickness (mm) No defined standards	3.1365 mm	3.31383 mm	Almost same thickness.
Hardness (4-10 kg/cm^2)	1.59	1.67	Both are <4 kg. Branded is closer than generic.
Friability (NMT 0.5-1% weight loss)	0.86%	4.83%	Weight loss is within standard for generic and deviated for branded.
Assay (90-110% purity)	96.18%	96.97%	Purity is within the standards.
Disintegration test (15min in water with 37°C)	3.16 min	2.37 min	Both are within standards.
Dissolution test (95-105% of drug release)	95.36%	94.68%	Dissolution is within the standards for generic and beyond standard for branded.
Determination of absorption maxima	243 nm	244 nm	Absorption maxima of both are close to each other.

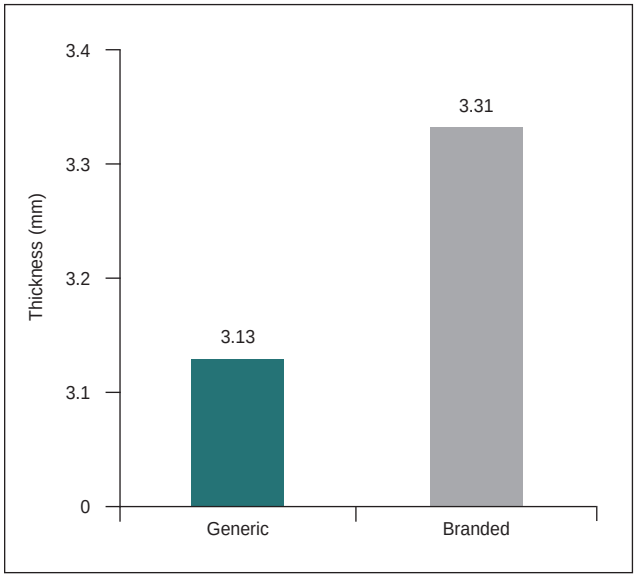


Figure 10. Atorvastatin thickness.

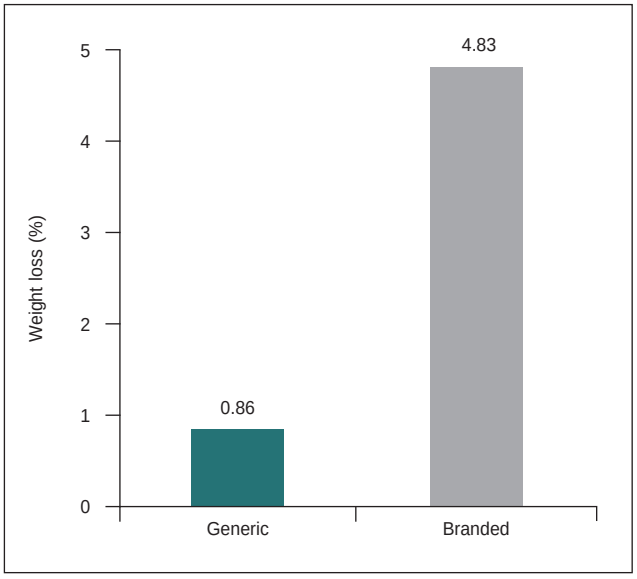


Figure 11. Atorvastatin friability.

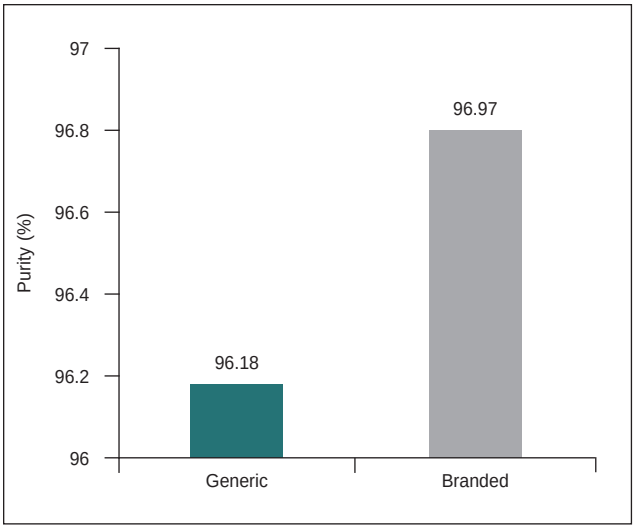


Figure 12. Atorvastatin assay.

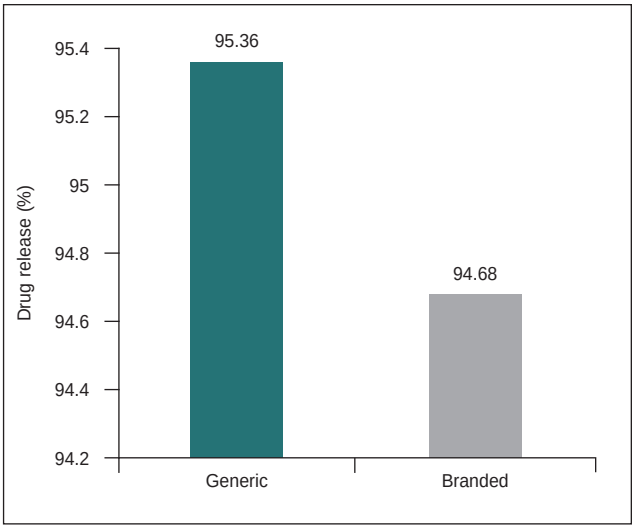


Figure 14. Atorvastatin dissolution test.

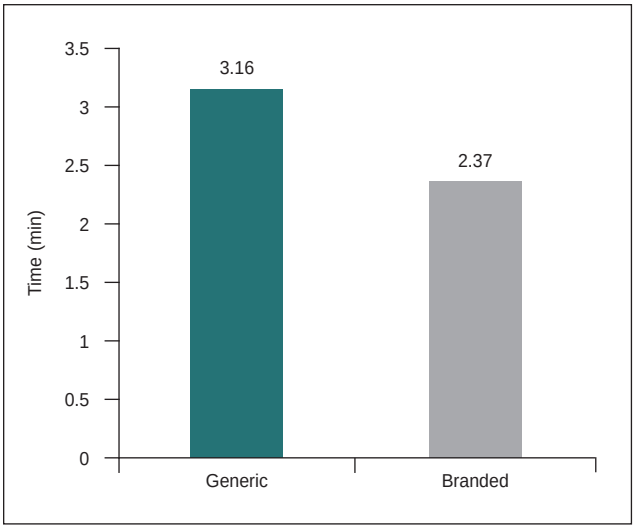


Figure 13. Atorvastatin disintegration test.

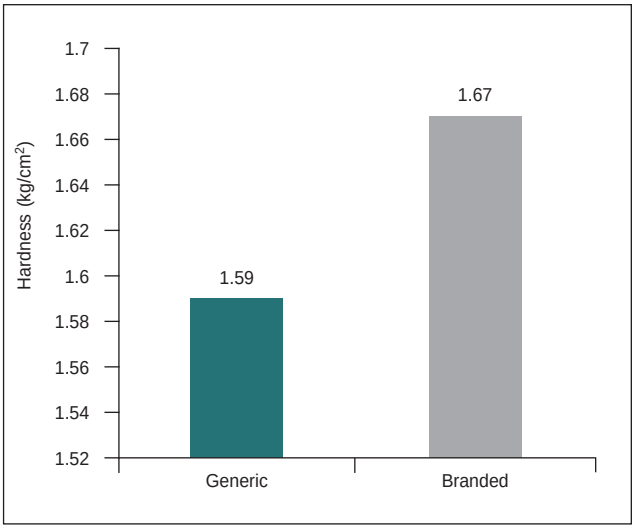


Figure 15. Atorvastatin hardness test.

CONCLUSION

This is a timely project wherein interest towards generic medicine is piling up in the healthcare market. In spite of completion of the patent period, the prices of branded medicines are still high. Most of the drugs have completed their patent period somewhere 30-50 years back. Still the branded drug manufacturing companies are pricing their products which were fixed along with Patent Royalty.

The scenario of the generic industry is different. The prices are fixed as per the cost work analysis of the manufacturer which does not include Patent Royalty. This is the reason why the generic formulations are cheaper than the branded ones. While the Indian pharmaceutical companies are playing a major role in the world generic market, the local markets are very discouraging.

Even our Prime Minister has been giving a big push to generic drugs to reduce out-of-pocket expenditure for consumers. The MCI directed the doctors to compulsorily write molecule or chemical name in prescriptions as against practice of writing brand names. This directive can be a game-changer for generic drugs in the country. The government ordered drug makers to print molecule names more prominently on their packs over brand names, in addition to issuing directive for drug stores to display generic drugs prominently.

Now, the time has come to focus the reality in branded medicine prices and on the quality standards of generic medicines at the same time.

A detailed comparative study was conducted on quality control parameters on generic and branded formulations pertaining to three drugs. The present study defined that the quality standards of generic formulations are no way inferior to those of branded formulations.

Wide publicity is required on behalf of generic drugs to swipe off false notions like "generics do not comply with the quality standards" among the public. Further comparative studies on all the drugs shall be taken up for a clear picture on the quality standards of generic formulations in the days to come.

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■■■■

WHO Abandons Opposition to COVID-19 Vaccination for Pregnant Women

The WHO has modified its guidance for pregnant women considering a COVID-19 vaccine. The agency has dropped the opposition to immunization for most pregnant women, unless they have a high risk.

WHO had previously stated that it did not recommend COVID-19 vaccination of pregnant women with Pfizer-BioNTech and Moderna vaccines, which was followed by commotion and disappointment expressed by experts. Several experts stated that WHO's earlier stance was not in line with the guidance provided by the US CDC and would eventually end up confusing pregnant women looking for clear advice on the subject. Although the vaccines have not been tested in pregnant women, but no harmful effects have been noted in animal studies. Additionally, the technology that has been used in the two vaccines is known to be safe, added the experts… (*ET Healthworld – NYT News Service*)

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#Data on file

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COMPOSITION: Each gram contains: Neomycin sulphate IP 5 mg, Bacitracin IP 250 units, Sulfacetamide USP 60 mg, Excipients q.s. **INDICATIONS: NEBASULF®** is indicated in treatment of topical bacterial infections caused by organisms sensitive to the antibiotic ingredients; e.g., conditions such as, boils, burns, wounds, skin grafts; otitis externa; gynecologic or general surgical procedures, and umbilical cord dressing. Dermatologic: Atopic, contact, stasis, and infectious eczematoid dermatitis; infectious neurodermatitis; eczema; anogenital pruritus. It may also be useful as an adjunct in certain pyodermas, such as impetigo, during specific systemic antibiotic therapy for these infections and prevention of secondary bacterial infections. **DOSAGE AND ADMINISTRATION:** Topical preparations should be kept in continuous contact with the infected area. Duration of treatment will depend on the nature and severity of the infection and may vary from a few days to several weeks. Since the causative organism may reappear if therapy is interrupted too early, treatment should be continued until healing is complete. Sprinkling Powder: Should be applied only topically and should not be introduced into closed body cavities. Application is as follows: After the skin is gently and thoroughly cleansed, the powder may be sprinkled directly onto the involved area or applied on a sterile gauze. In the treatment of external otitis, it may be insufflated into the external auditory canal. Application should be repeated at least 2 or 3 times daily. **CONTRAINDICATIONS:** NEBASULF® is contraindicated in individuals with a known or suspected sensitivity to Neomycin, Bacitracin, or to sulfonamides. Do not use in the external ear canal, if the eardrum is perforated. **WARNINGS AND PRECAUTIONS:** Because of the potential hazards of nephrotoxicity and ototoxicity due to Neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration, and other extensive conditions where absorption of Neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. When using Neomycin-containing products to control secondary infection in chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including Neomycin. The manifestation of sensitization to Neomycin is usually a low-grade reddening with swelling, dry scaling, and itching; it may manifest simply as a failure to heal. During long-term use of Neomycin-containing products, periodic examination for such signs are advisable, and the patient should be told to discontinue the product, if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient, thereafter. As with any antibacterial preparation, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If this occurs, treatment should be discontinued, and appropriate therapy instituted. **DRUG INTERACTIONS:** Decreased effect is noted with silver and gentamicin (antagonism). **PREGNANCY AND LACTATION:** The amount of systemic absorption following topical administration is not known. Use during pregnancy, only if benefits outweigh the risk. There is no data available on excretion in breast milk. **ADVERSE REACTIONS:** Sensitivity, especially to the Neomycin ingredient, may develop after continuous, chronic therapy. If itching, burning, or inflammation follows application, usage should be discontinued. **SOURCE:** Prepared based on full prescribing information (version 01) dated 4th April 2019

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Reversing Type 2 Diabetes Through Functional Medicine

PRITI NANDA SIBAL

ABSTRACT

Diabetes is one of the biggest global health emergencies of the 21st century. Overall, 425 million people worldwide are estimated to have diabetes, with India being home to the second largest number of people suffering with diabetes. A recent analysis showed that diabetes-related complications are continuously on the rise. These complications affect almost all systems of the body leading to retinopathy, neuropathy, nephropathy, cardiovascular disorders, diabetic foot, depression, anxiety and even eating disorders in diabetes patients, severely affecting the patient's quality-of-life. Traditional approach towards treating type 2 diabetes does not try to alter the course of diabetes at the prediabetes stage. It works on the symptoms, and as a result, the basic pathology keeps on getting intense and therefore, the number and dose of medicine keeps on increasing every few years. Functional medicine provides a holistic approach towards managing diabetes and reducing the complications associated with it. This review discusses the functional medicine approach, detailing the early diagnosis approach, preventive strategy, regular monitoring of blood glucose parameters and treatment approach of diabetes including diet management, exercise, functional foods, nutritional supplements and genetic and lifestyle interaction.

Keywords: Functional medicine, diabetes, reverse diabetes, diet, stress, exercise, nutritional medicine, functional foods

Diabetes is one of the largest global health emergencies of 21st century. Overall, 425 million people worldwide are estimated to have diabetes, with almost 79% living in low- and middle-income countries. India is home to the second largest number of adults living with diabetes worldwide, after China. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths.

Diabetes is an ever-growing problem, primarily due to a lack of lifestyle education and physical activity as well as the consumption of high-calorie, low-nutrient, processed foods. Diabetes has various and often devastating complications such as heart disease, stroke, high blood pressure, nerve damage, kidney damage, eye damage, foot damage, hearing impairment, skin conditions such as bacterial and fungal infections and even Alzheimer's disease. With 1 out of 11 people suffering from diabetes, the disease disrupts all aspects of human physiology and increases the risk of cardiovascular disease, cancer, cognitive decline and virtually every other disease.

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Functional medicine plays a crucial role in managing and reversing diabetes by applying itself to laboratory testing, performing an extensive evaluation of the patients' overall lifestyle and health history leading to detection of issues, which can be reversed using intensive lifestyle changes. Functional medicine can control the blood glucose levels, as well as help in reducing many other linked health issues of the patient. Functional medicine is successful in not only optimizing glycosylated hemoglobin (HbA1c) and blood glucose levels, but also reversing diabetes completely.

CONVENTIONAL MEDICINE APPROACH

In conventional approach to diabetes treatment, inadequate time is spent on identifying the root cause of the disease. In traditional practice, the common approach is to wait till the patient is in later stages of diabetes and not much is done to alter the course of the disease in its early (insulin resistance) or prediabetes stage when the body is more responsive to diet and lifestyle changes.

FUNCTIONAL MEDICINE APPROACH TOWARDS DIABETES

Functional medicine approach works by applying itself to detailed laboratory testing, performing an extensive evaluation of the patient's overall lifestyle and health

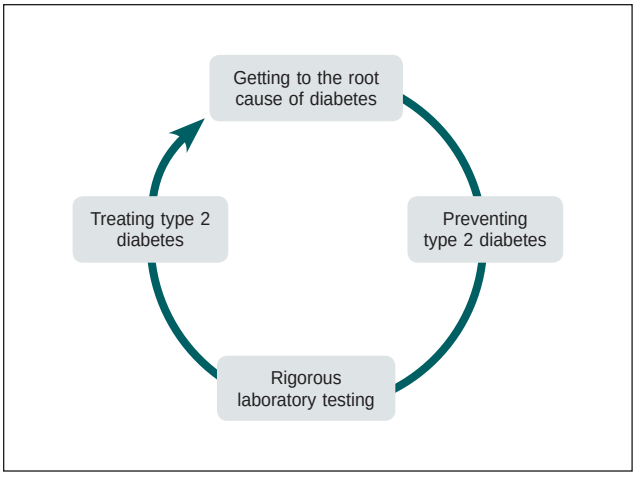

Figure 1. Functional medicine approach for diabetes management.

history leading to detection of issues, which can be reversed using intensive lifestyle changes. In patients who are already diagnosed with type 2 diabetes, functional medicine approach tends to look for the root cause and correct it, thereby alleviating many (if not all) symptoms associated with diabetes (Fig. 1).

Getting to the Root Cause of Diabetes

Blood glucose is a symptom of diabetes and not the cause of diabetes. Hence, it is important to understand that treating only the symptoms will not be helpful in alleviating diabetes. It thus becomes imperative to detect the primary cause of diabetes.

Insulin resistance

Insulin is an important hormone released by β-cells in the pancreas with one of its key functions being balancing the blood glucose levels in the body. To achieve blood glycemic control, insulin undergoes a process which allows the glucose floating in the blood to efficiently get absorbed into individual cells throughout the body (muscle, fat, liver, etc.). In the presence of insulin resistance, this process is disrupted, leading to a release of more insulin, to ensure that the glucose is absorbed in the body cells. However, as the blood glucose increases owing to lifestyle, genetics, toxins or mitochondrial function impairment, the β-cells are unable to produce more insulin, which causes an excess build-up of glucose in the blood. This excess glucose then damages cells throughout the body, and these symptoms present as diabetes complications in the body.

Chronic stress

Chronic stress is another factor leading to insulin resistance which in turn causes type 2 diabetes. Stress increases cortisol levels in the body, which increases blood glucose levels. In case, the stress is temporary, there is no problem; however, if the stress persists due to a high-stress work environment, or disturbed family life, then the persistently elevated cortisol causes persistently elevated blood glucose and the β-cells are unable to secrete adequate insulin. High perceived stress is associated with insulin resistance and a significantly increased risk of type 2 diabetes in adults.

Lack of sleep

Research has shown that sleep deprivation is also linked to insulin resistance. A study conducted among 9 healthy subjects (5 men and 4 women) has shown that partial sleep deprivation during only a single night induces insulin resistance in multiple metabolic pathways in healthy subjects. This physiological observation is of relevance for variations in glucose regulation in patients with type 2 diabetes. Sleep deprivation increased plasma nonesterified fatty acid levels.

Microbiome

Another theory suggests that an imbalance in the body's flora and fauna leads to an overgrowth of harmful bacteria carrying lipopolysaccharide. Lipopolysaccharide release has also been associated with insulin resistance. Research has also shown that patients with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome.

Methylation status

Epigenetic modifications, including DNA methylation, have been identified as one mechanism by which the environment interacts with the genome and there is evidence that alterations in DNA methylation may contribute to the increased prevalence of type 2 diabetes.

Smoking

Cigarette smoking is a well-known risk factor in many diseases, including diabetes. Many studies have reported the unfavorable effects of smoking on diabetes mellitus. Smoking increases the risk of developing diabetes, and aggravates the micro- and macrovascular complications of diabetes mellitus. Smoking is associated with insulin resistance, inflammation and dyslipidemia, but the exact mechanisms through which smoking influences diabetes mellitus are not clear. However, smoking cessation is one of the important targets for diabetes control and the prevention of diabetes complications.

Genetic propensity to diabetes

Type 2 diabetes has a strong link to family history and lineage, although it also depends on environmental factors. The underlying genetic basis for mortality likely involves complex interactions with factors related to ethnicity, type 2 diabetes and body weight. Type 2 diabetes is partly genetically determined. Genetic factors that increase type 2 diabetes susceptibility may also raise mortality risk through type 2 diabetes or its related complications.

Preventing Type 2 Diabetes

Functional medicine takes a proactive approach in preventing type 2 diabetes. A detailed testing allows functional medicine practitioners to identify and initiate the reversal of problematic changes such as insulin resistance much sooner than the standard care in conventional approach of diabetes management. Functional medicine has laid down completely new standards for allowing early detection of diabetes so that it can be easily nipped in the bud.

Detailed Laboratory Testing

Functional medicine follows a detailed lab testing and has more sensitive parameters than other conventional diagnostic methods. It is a well-known fact that conventional lab ranges for blood glucose and HbA1c which are considered by clinicians when screening for diabetes allow for quite high range of blood sugars before diabetes is diagnosed.

Current recommendations from the American Diabetes Association for laboratory values that qualify a patient for type 2 diabetes include:

- HbA1c: <7.0%
- Two-hour postprandial blood glucose: <180 mg/dL
- Fasting blood glucose: 80-130 mg/dL.

However, functional medicine looks for early warning signs such as mild elevations of glucose or of insulin resistance. Early markers for type 2 diabetes and related conditions in functional medicine are:

- Fasting glucose: 84 mg/dL
- Elevated triglyceride level
- Elevated uric acid level
- Low high-density lipoprotein (HDL)
- Elevated low-density lipoprotein (LDL)
- HbA1c: >5.4%
- Increased insulin or C-peptide levels (for long-term average insulin production)
- Antibodies such as glutamic acid decarboxylase (GAD65), pancreatic islet cells
- Increased waist size (>40 inches in men; >35 inches in women)
- Waist-to-hip ratio >0.85 in females and >0.90 in males
- Elevated blood pressure.

All these early warning signals, help in early diagnosis of diabetes or insulin resistance, hence curbing the progression to diabetes. Timely approach targeting the cause of this variation helps in completely reversing the condition and helps patients in regaining optimal health conditions.

Treatment of Type 2 Diabetes

In contrast to conventional medicine approach, functional medicine takes the path of supporting diet and lifestyle changes in the patient as the primary treatment for type 2 diabetes (Fig. 2) and optimizing the laboratory markers.

Under the vestiges of functional medicine, the patient is educated at length about food and nutrition, lifestyle changes and balancing laboratory markers through various scientific approaches, a typical visit averaging about between half an hour to 90 minutes.

Healthy gut

Research has shown that an altered, inflammatory gut microbiota is of utmost importance in the development of type 2 diabetes. A recent study showed that metformin has an effect on the gut microbiota; the drug increases levels of *Akkermansia muciniphila*, which is a commensal gut bacterium, associated with reduced inflammation and improved metabolic health. This supports the fact that the gut microbiota plays a pivotal role in type 2 diabetes.

Several prebiotics and probiotics have been investigated for their antidiabetic and gut health-promoting effect.

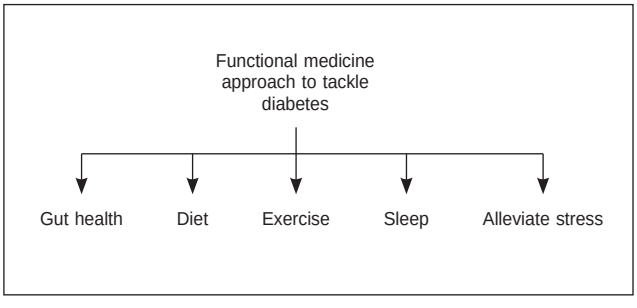

Figure 2. Components of functional medicine approach to manage diabetes.

A prebiotic fiber found in mushrooms and konjac root has been found to boost the blood glucose levels, reducing effects of metformin. Similarly, inulin, a prebiotic found naturally in chicory, garlic, onions, leeks and asparagus, reduces fasting blood glucose and promotes a more metabolically healthy gut microbiota. Certain probiotic strains such as Lactobacilli and Bifidobacterium also improve biomarkers of inflammation and oxidative stress in type 2 diabetes and lower fasting blood glucose by promoting an anti-inflammatory gut microbiota.

Diet

Low-carbohydrate diet

A persistently growing body of research has indicated that low-carbohydrate diets are superior to high-carbohydrate diets for the treatment of type 2 diabetes. A recent systematic review and meta-analysis of 18 randomized controlled trials has found that reducing dietary carbohydrates produces significant improvements in HbA1c, triglycerides and cholesterol, while also lowering patient's diabetes medication requirements.

Various large-scale clinical studies have compared the effectiveness of low-carbohydrate diet with high-carbohydrate diet to treat diabetes. The results of these studies have again reiterated that low-carbohydrate diets consistently outperform high-carbohydrate diets for the management of type 2 diabetes. In addition, it also produces more significant improvements in blood glucose stability and lipid profiles and significantly reduces the need for medications. Along with quantity, it is also important to refine the quality of carbohydrates being consumed by the patients.

Low glycemic index diet

A meta-analysis of six small studies (n = 202) with short duration, revealed that overweight or obese people on low glycemic index diets lost more weight and had better improvement in lipid profiles than those receiving other diets.

Cyclic ketogenic diet

Cyclic ketogenic diet has emerged as an effective alternative diet that relies less on medication, and may even be a preferable option when medications are not available. This form of keto diet helps patients follow it more consistently and reap best and long-term results. The ketogenic diet substantially reduces the glycemic response that results from dietary carbohydrate as well as improves the underlying insulin resistance. Results of a study demonstrated that low-carbohydrate, keto diet resulted in significant improvement of glycemia, as measured by fasting glucose and HbA1c in patients with type 2 diabetes. An important point to note here is that this improvement was observed while diabetes medications were reduced or even discontinued. Along with this, participants also experienced moderate reductions in body weight, waist circumference and percent body fat. Another study has also shown that Mediterranean diet was associated with better glycemic control and cardiovascular risk factors than control diets, including a lower fat diet, suggesting that it is suitable for the overall management of type 2 diabetes.

Mediterranean diet

In a randomized, single-blind controlled trial, it was shown that a Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome.

Nutraceuticals in insulin resistance syndrome

Nutraceuticals or functional foods such as plant proteins have been shown to improve insulin resistance and reduce triglyceride secretion. Pro- and prebiotics, that are able to modify intestinal microbiome, reduce absorption of specific nutrients and improve the metabolic handling of energy rich foods. Lastly, specific nutraceuticals have proven to be of benefit such as red-yeast rice, berberine, curcumin, acai, berry antioxidants, *Ginkgo biloba*, green tea as well as vitamin D. All these can improve lipid handling by the liver as well as ameliorate insulin resistance.

Micronutrients

Micronutrient recommendations for a diabetes patient include chromium, vitamin D, magnesium, CoQ10 and alpha-lipoic acid. Alpha-lipoic acid has been shown to be beneficial in the treatment of peripheral diabetic neuropathy. Benefits of magnesium supplementation on metabolic profile in diabetes patients have been found in many clinical studies.

Exercise

It is a well-known fact that a sedentary lifestyle is a significant risk factor for type 2 diabetes, so exercise should be a central part of any treatment plan for the disease. Research has indicated that walking for just 30 minutes a day reduces the risk of type 2 diabetes by approximately 50%. High intensity interval training also appears beneficial as it reduces fasting blood sugar, HbA1c and cardiovascular complications in type 2 diabetes and is more effective than continuous aerobic activity for improving blood sugar control.

In addition to increased exercise, reducing sedentary time in daily life is also essential. Alternate sitting with working at a standing desk or treadmill desk, breaking up prolonged sitting with standing or walking has been shown to improve the post-meal blood glucose response in those at risk for diabetes.

Maintaining sleep hygiene

Research has shown that short sleep duration or sleep loss may promote type 2 diabetes by interfering with energy metabolism and increasing insulin sensitivity. Sleep loss also impairs satiety, triggering cravings and overconsumption of sugary processed foods that increase the risk of diabetes. Obstructive sleep apnea, a common cause of sleep loss, promotes type 2 diabetes by inducing hypoxia, which in turn impairs insulin production by pancreatic β-cells.

Functional medicine focusses on strategies that correct obstructive sleep apnea, reduces severity of apnea and improves sleep quality and duration.

Stress management

Research has shown that reducing psychological stress can improve blood sugar management in type 2 diabetes. Functional medicine adopts an approach to alleviate patient's chronic stress and improve his overall health as well as reverse diabetes condition. Meditation, yoga, laughter therapy and breathing exercises have been found to reduce fasting blood glucose and post-meal glucose hike in diabetes patients. Functional medicine practitioners offer guided meditation, breathing exercises and relaxation techniques to the patients to alleviate stress.

Pharmacological management

Although currently there are no Food and Drug Administration (FDA) approved medications specifically for the treatment of insulin resistance, the pharmacological agents that are often prescribed for insulin resistance in some patients include metformin and thiazolidinediones. Insulin is also used for some cases of insulin resistance. Metformin is a biguanide insulin sensitizer that is used as a first-line drug.

CONCLUSION

Poor diet, a sedentary lifestyle, inadequate sleep, chronic stress, gut dysfunction and environmental toxins, genetics, toxic thoughts and disturbed mitochondrial function play a significant role in causing diabetes. Functional medicine is a science-based approach to preventing and treating diabetes that is focused on diet and lifestyle changes, and is the most effective first-line strategy for managing type 2 diabetes. It is an effective way to prevent, treat and manage type 2 diabetes. Reversing type 2 diabetes is no more a dream now.

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■■■■

Higher Dietary Fiber Intake Linked to Lower Depression Risk Among Young Women

Higher dietary fiber consumption may be linked with a reduced risk of depression among premenopausal women, suggests new research. Researchers looked into data obtained from nearly 6,000 pre- and postmenopausal women. Among premenopausal women, dietary fiber intake was found to be higher among those who did not suffer from depression compared to those who had the disorder, in a dose-dependent manner. No association was found between higher fiber intake and depression risk among postmenopausal women. The study was published online in *Menopause*. Researchers noted that the estimated mean dietary fiber intake was significantly higher among women who did not have depression, compared to those with depression (14.07 ± 0.11 g/1000 kcal/d vs. 12.67 ± 0.45 g/1000 kcal/d; p = 0.003)… (*Medscape*)

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Targeting Immune Switches/Molecules for Cancer Management – Developments in Nanotechnology

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ABSTRACT

Immunity is an inherent phenomenon in higher animals, comprising of two major components - innate and adaptive immunity. The preponderance of research work and scientific findings have proved that immune system is centrally involved in all major diseases and disorders of humans. However, the approaches to program immune system are partially studied and constitute a complex phenomenon. On the contrary, modulating immune system may provide substantial relief in disease management by targeting selective molecular switches with minimal physiological losses. As the immune system is highly regulated and complex, the reprogramming of such events was highly difficult in previous times. However, recent developments in bioengineering, precisely in nanoscience and nanotechnology, enabled us to target selectively key immune molecules to combat life-threatening diseases and disorders. Several diseases, such as cancer, neurological disorders (including neurodegenerative) and genetic diseases, can be cured if diagnosed at an early stage. In this review, we would like to emphasize the potential of nanotechnology in the management of major human diseases by targeting immune molecules in context with cancer management. We also highlight the scope of nano designs in disease management. The article provides an overview of nanotechnology not only in disease management but in diagnostic development as well.

Keywords: Immunity, innate and adaptive immunity, nanotechnology, nano design, drug targeting and delivery

INTRODUCTION TO NANOTECHNOLOGY

Nanotechnology is an interdisciplinary area comprising of bioengineering, chemistry and physical sciences intended to develop novel material, tools and technologies for various commercial applications in different areas including healthcare, industry, agriculture and environmental studies. Nanotechnology deals with design, synthesis, characterization and application of materials and devices with the smallest functional organization, at least in one dimension, on the nanometer scale or one billionth of a meter. In recent times, nanotechnology and nanotechnology-based designs have shown promising results in healthcare. At this scale, these designs are capable of entering into the cell for the diagnostic and therapeutic purpose. The nanotechnology-based innovation is being used for fluorescent biological labels, drug and gene delivery, bio-detection of pathogens, detection of protein, probing of deoxyribose nucleic acid (DNA) structure, tissue engineering, tumor detection, separation and purification of biological molecules and cells, magnetic resonance imaging (MRI) contrast enhancement and phagokinetic studies. Considering such vast application of nanotechnology-based designs and approaches, the modern healthcare utilizes these services on a large scale with promising results as well.

The core player in nanotechnology is design of nano cargoes for intended uses including both diagnostic and therapeutic. The average size of a eukaryotic cell is 10-100 μm and nano designs are far smaller and can easily enter into the cell. These designs can enter into the cytoplasm and can travel in different cellular compartments, including the nucleus. The affinity of nanoparticle depends on the material from which it is synthesized. However, the physiochemical properties of these nano designs can be controlled by several other parameters, including the method used for synthesis/design, the material used, additives and

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fabrication. Based on these properties, nano designs being used in medicine for diagnostic and therapeutic purposes can be - Nanotubes, nanoparticles, quantum dots, liposomes, immune liposomes, nanopores, dendrimers, aptamers, nanoshell and magnetic nanoparticles (Table 1).

These nano designs have a unique role and are widely used in medicine including cancer treatment. Studies have demonstrated nanotubes are ideal and most effective drug delivery vehicles for cancer management as they allow the drug to selective tissue. Nanoparticles and quantum dots are capable of penetrating into deeper tissues as conventional drugs fail to reach the core of cancer tissue where cells are packed tightly. The liposome and immune liposome are capable of carrying a large amount of anticancerous drug to the targeted tissue. The aptamer is a highly sensitive nano design for diagnostic purpose. The nanopores are effective in allowing drugs into the subcellular compartment. The nanoshell allows a drug cargo for sustained release and has proven much effective to provide drug plasma concentration. The magnetic nanoparticles are an ideal choice for controlled release of anticancerous drugs and for diagnostic applications. These designs are much effective in case of brain tumor where conventional drugs and approaches fail as neuronal tissue possesses additional protection called blood brain barrier.

IMMUNE SWITCHES AND MOLECULES

The immune switches and molecules summarize some immune players that participate in the onset of cancer and progression. There are several genes called as oncogenes, present in the human genome as proto-oncogenes that play a central role in cancer development. Further, immune players including interleukins, cytokines and chemokines are essential for cellular growth and development. Additionally, cell cycle regulatory proteins, called as cyclins, are keys proteins that regulate the cell cycle. Additionally, several transcription factors play a central role in the expression of immune modulators that trigger a cell to opt abnormal cell division and grow as cancerous tissue. The inflammatory mediators are also vital in cancer development under abnormal expression and functioning. The nuclear factor kappa B (NF-κB) is a major transcription factor for various immune and inflammatory mediators affecting some metabolic pathways. The major immune switches and molecules involved in cancer development are as follows (Table 2):

Cell Cycle Regulatory Molecules

- Cyclins - Cyclins A, B, D and E
- Cyclin-dependent kinase (CDKs) - CDK4 and CDK6
- Cyclin-dependent kinase inhibitors

Proto-oncogenes

- ABL
- HER
- MYC
- Ra AS
- RET

Tumor Suppressor Genes

- Rb
- p53
- INK4A
- Bcl^2
- $BRCA^2$

Transcription Factors

- NF-κB
- IRF
- Rel
- GR
- NFAT
- AP-1

Immune Modulators and Messengers

- Interleukins
- Cytokines
- Chemokines

The development of cancer is a complex phenomenon and involves several factors including genetic and environmental. The cancer development demonstrates the abnormal function of all these factors listed above. A cell opts abnormal cell division either in the presence of carcinogen and/or abnormal functioning of cellular molecules/switches. There are several repair mechanisms running parallel to revert abnormal cell division. The caspase mechanism selectively targets such cells and kills them before they undergo cancerous tissue development. There are two stages of cancer development - one results in benign cancer and second, metastasis, i.e., spreading of cancer cell and development of secondary cancer. The immune switches and molecules act as triggers often to speed-up

Table 1. List of Nano Designs for Cancer Diagnosis and Drug Delivery

Nano designs	Applications
Nanotubes	Anticancer drug delivery
Nanoparticles	Anticancer drug delivery and diagnostics
Quantum dots	Diagnostics application
Liposomes	Drug delivery including chemical-based and biological-based (DNA, RNA and protein-based drug)
Immune liposomes	Drug delivery and diagnostics, drug delivery chemical-based and biological-based (DNA, RNA and protein-based drug)
Nanopores	Selective drug delivery for drug-resistant tumors
Dendrimers	Diagnostic development
Aptamers	Diagnostic development
Nanoshell	Drug delivery, offer a large volume of anticancer drugs
Magnetic nanoparticles	Diagnostics and drug delivery

Table 2. Immune Switches and Molecules with their Involvement in Cancer Development

Immune switches	Role in cancer development
NF-κB	Regulates inflammatory mediators and other molecules as major transcription factor
Bcl	Proto-oncogene plays central role in cancer development on overexpression
Chemokines	Key immune mediators for cross-talk among cells and act as messenger
Cytokines	Key bioactive immune mediators regulate various cellular and subcellular events
Interleukins	Key bioactive immune mediators regulate various cellular and subcellular events
IRF	Transcription factors
p53	Proto-oncogene upon activation leads to cancer development
Rb	Proto-oncogene upon activation leads to cancer development
Interferon	Immune mediator expressed during viral infection can lead to abnormal cell growth and cancer development

cancer development under abnormal expression. Further, inflammatory mediators and carcinogens act as a catalyst for cancer development. There are several tumor suppressor genes to control abnormal cell division and cancer development. In many cases, abnormal expression of immune molecules blocks the functioning of tumor suppressor genes. The cancer cell has unique cell division pattern and utilizes massive amount of nutrients for rapid growth and development of the tumor. There are several studies that demonstrated abnormal expression of immune mediators and caspase components in cancer cells. The immune molecules behave entirely different in cancer cells, and cancerous tissues mostly support the development of the tumor. The metastasis is the chronic stage of cancer with spreading of cancerous tissue. There are several molecular signals for metastasis, and immune mediators are a key one. These mediators activate benign tumor and spilt cancerous tissue. The metastasized cells travel to another part of the body via systemic flow and grow as secondary cancer.

Figure 1 depicts the factors involved in cancer development and the role of immune switches/molecules in regulation of other factors.

CANCER – PREVALENCE AND CAUSES

Cancer is a leading cause of death and physical deformity worldwide. As per World Health Organization (WHO) report 2016-17, there is a rise in cancer development by 15-20% annually in various parts of world population. On the world map, the USA and Western Europe have the largest number of cancers per country population. Further, the Soviet Union and Austria are leading in different types of cancer cases. Asia and Africa have a higher percentage of new cases of cancer but comparatively less in percentage from a developed nation. Considering overall statistics of cancer on world map, breast and cervical cancer are leading, followed by pancreatic cancer, gastric, prostate, oral and colorectal cancer. Lung cancer and leukemia are also prevailing with a much higher rate. More than 10 million people die annually from different types of cancers, and lack of precise diagnostic methods and therapeutics has enhanced global mortality caused by cancer. Males and females have a different rate of cancer development. Females have comparatively much higher cancer cases due to many reasons, including complex hormonal mechanism and change in immune parameters at every stage of life. In case of females, breast and cervical cancer are prevailing worldwide. One of the major causes of these two classes of cancer

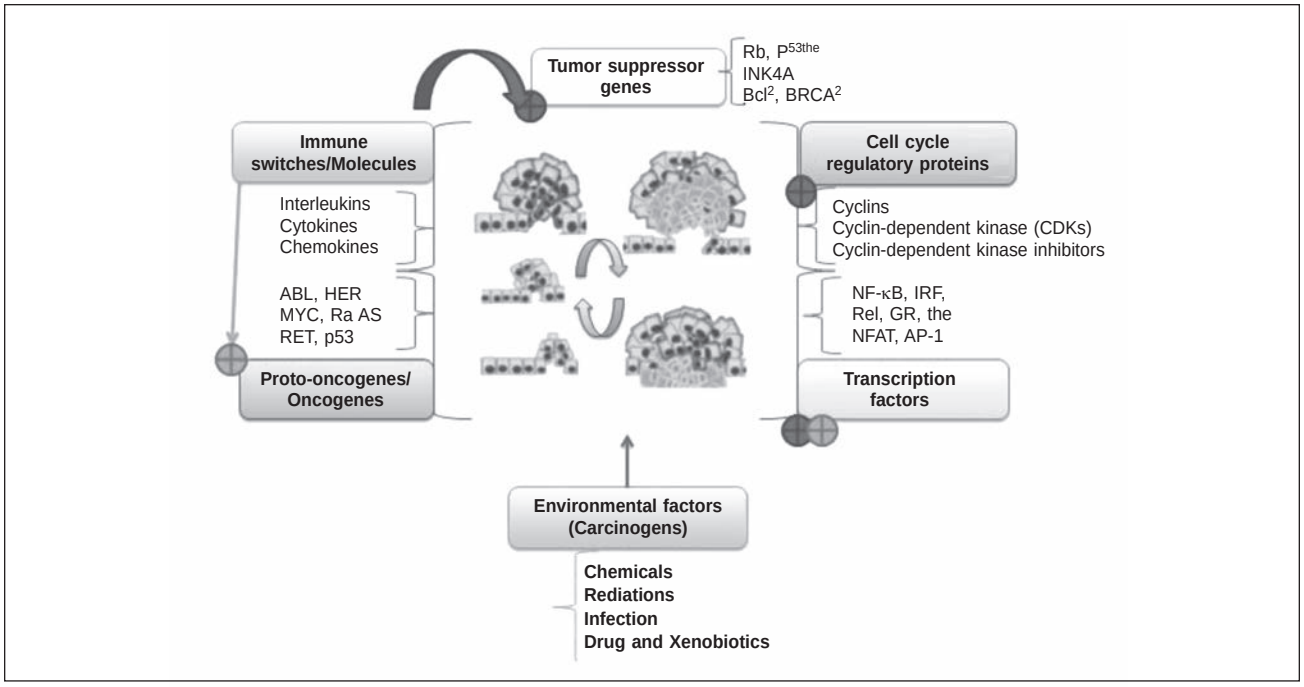

Figure 1. Factors involved in cancer development and role of immune switches/molecules in regulation of other factors.

in female population is altered sex hormone level from puberty to menopause. However, there are several other factors and causes for cancer development including genetic history, daily lifestyle, consumption of tobacco and drugs. On the contrary, cancer prevalence in male population is high for prostate and gastric cancer. Apart from these, there are several classes of cancer in both male and female populations, including oral cancer, liver cancer, gastric cancer and leukemia and brain tumor. Acute lymphoblastic leukemia (ALL) is highly complex and difficult to cure as immune cells themselves are involved in cancer development. In India, oral cancer is prevailing at a much higher rate as India is the leading country for tobacco consumption. Infections are key environmental mutagens that cause different types of cancer, including cervix cancer in females. Here, human papillomavirus is the key infection that causes cancer in young women.

ROLE OF THE IMMUNE SYSTEM IN CANCER MANAGEMENT

Immune system collectively, both innate and adaptive, plays a key role in maintaining homeostasis in living tissues by regulating various metabolic events. In addition to fighting against foreign infections, the immune system also makes surveillance in abnormal growth and development of a tumor. The immunotherapies are future medicines not only for cancer but also for several other diseases. There are several developments in cancer immunotherapy that have shown promising result in early diagnosis and treatment of cancer. The recent development of cancer immune therapy involves adaptive T-cell therapy based on chimeric antigen receptors (CARs) and checkpoint blockade. The former, CAR T-cell therapy, still under clinical evaluation, is based on genetically engineering patient's T-cells with CARs that recognize tumor antigens. These CAR T-cells are then expanded *in vitro* and infused back in patients, where they are likely to recognize and kill cancer cells. Checkpoint blockade therapies, on the other hand, work by inhibiting pathways that keep the duration and strength of immune system in check. The recent approval of two checkpoint blockade therapies targeting the receptors cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) have come on the back of several successful clinical trials where treatment with checkpoint blockade inhibitors has resulted in striking T-cell function restoration in melanoma, renal cell carcinoma and lung cancer.

Further, a highly immunosuppressive micro-environment under the influence of cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-2, along with immunosuppressive cells such as $Foxp3^+$ T (regulatory T-cells) myeloid-derived suppressor cells (MDSCs) and M2-type macrophages, or combinations thereof, keeps such autologous immune response in check. Moreover, through intricate

immunoediting mechanisms, including antigen shedding, negative selection of antigenic cancer cells, down-regulation of major histocompatibility complex class I (MHC-I) molecules and turning off activated T-cells via negative regulators such as PD-1, cancer cells evade immunosurveillance and the tumor prevails. The genome editing technologies such as clustered regularly-interspaced short palindromic repeats (CRISPER)/Cas are effectively being used to reprogram immune modulators and switches centrally involved in onset and progression of cancer. Further, gene silencing techniques based on microRNA, RNA interference and negative regulators are being used to regulate expression of oncogenes. At the same time, using genome editing technology such as CRISPER/Cas is being used for overexpression and regulation of tumor suppressor genes. The immune mediators including chemokines, interleukins and cytokines with immense biological activities, are being reprogrammed to control and inhibit the growth of cancerous tissue.

NANOTECHNOLOGY IN CANCER MANAGEMENT

The nanotechnology emerged as major scientific findings in cancer management offered its potential in diagnostics development and precise drug delivery. One of the achievements in recent times is the development of real-time diagnostic methods. Nanotechnology played a vital role in developing various probes and fluorescence molecules tagged with nanoparticles/nano designs capable of entering into subcellular compartments. The cy3/cy5, red fluorescent and green fluorescent proteins are being used extensively for real-time monitoring in cancer diagnostics. The ability of nanoparticles and other nano designs to stand in adverse environment with intact physiochemical properties enables them for being used in robust diagnostics development. With the advancement of nanotechnology, we are capable of developing ready to use diagnostic tools and kits for various cancers and other diseases as well. It can detect even a single cancerous cell *in vivo* and deliver the highly toxic drugs to the cancerous cells. Nanoshells, carbon nanotubes, quantum dots, magnetic nanoparticles, nanowires, dendrimers and recently synthesized nanosponges are some of the materials used for cancer detection. Using specific cross linkers, such as specific antibodies against cancer cells, individual cancer cells can be located. With the aid of a novel set of lipid-coated, targeted quantum dots a method for quantifying multiple specific biomarkers on the surfaces of individual cancer cells was also developed.

This approach to quantitative biomarker detection stands to improve the histopathology methods used to diagnose pancreatic and other cancers and enable the development of methods to spot cancer cells circulating in the bloodstream. Certain nanomaterials can also deliver cancer drugs at the site so the drug toxicity can also be reduced. The second advancement in cancer management in context with nanotechnology is precise drug delivery.

The efficacy of any therapeutics depends on two major factors - one pharmacokinetic and second pharmacodynamic properties. Several drugs fail to offer aimed therapeutic response due to lack of pharmacokinetic and pharmacodynamic features. The nano designs are capable of entering into deeper tissues and are reported ideal for tumor tissue. The inside environment of a tumor is highly complex and many times, drugs delivered with conventional approaches fail to reach the core of cancer tissue, which further results in secondary cancer. The nano designs are useful not only for delivering drugs to deeper tissue but also carry a large volume of recommended drugs. The nano design, such as liposomes and nanoshell, can accommodate a bulk amount of antitumor drugs and deliver for a long period. Further, carbon nanotubes (CNTs) provide an ideal path for selective drug delivery without affecting healthy cells. Similarly, immune liposomes are advanced nano designs that find target tissue with antigen antibody recognition pattern. Further, nanopores are a unique design that offers drug delivery from one cell to other and among two tissues selectively. Considering modern cancer therapeutics, nanotechnology is playing a central role in cancer management not only in drug delivery, but also in developing precise diagnostics.

CONVENTIONAL VERSUS IMMUNE THERAPY

The traditional approach for caner management entirely depends on chemotherapy and radiation therapy. Surgery is old and least preferred method for cancer treatment and mainly used for removal of cancerous tissue. The conventional method utilizes a large number of cytotoxic drugs, which nonspecifically target healthy cells as well. Chemotherapy is not recommended for blood cancer and similar tissue cancers where there will be losses of mature immune cells that may provoke several other infections. Radiation therapy is much effective if used selectively. There are several approaches for radiation therapy, including using rays directly, precisely gamma rays. The modern radiation therapy depends on

the administration of radioisotopes, and these radioisotopes are targeted for a selective tissue. These radioisotopes release radiations at the targeted site and kill cancerous cell. All these approaches are associated with several limitations; including side effects, cellular and tissue toxicity, nonspecific cell death, hepatic and renal damage. All these conventional methods are effective in the early stage of cancer and offer only symptomatic relief. There is a high prevalence of secondary cancer and rapid metastasis as well. Further, such therapies are not recommended for several classes of cancers including ALL as there will be massive loss of immune cells.

On the contrary, immune therapies are highly selective and offer therapeutic activity against cancer precisely. The immune therapies for cancer provide a complete cure rather than symptomatic relief. As the immune molecules and approaches for immune therapy are highly selective for each other, there is the least chance of nonspecific cell damage. The cutting-edge technologies and innovations in bioengineering and nanotechnology find scope for targeting molecular pathways involved and selective drug delivery. There are several immune players including interleukins, cytokines and chemokines that play a central role at the beginning of cancer and progression, including metastasis. Additionally, several genes, called oncogenes, trigger a cell to opt cancerous pathway. The immune therapy for cancer involves regulation of immune player synthesis and release, expression of oncogenes and cross talk among oncogenes with immune players. Though the exact cause of cancer remains a big question and remains unresolved, targeting immune molecules and switches seems more effective and reliable in cancer management.

PROSPECTS

Cancer remains an unsolved human disease affecting a large number of populations across the globe. There are numerous kinds of cancer/tumor with complex molecular biology that are difficult to study and find a cure. With the increasing cases of cancer and new kinds of cancer, much emphasis is given to research and development. The researchers worldwide are looking to understand the molecular mechanism of precise cancers. There is much effort in developing molecular diagnostics for early detection to enable a precise and robust therapeutic approach. Hence, several genes called proto-oncogenes, and their expression profile has been studied. The effect of a carcinogen on the expression of proto-oncogenes is crucial and well-studied. In recent times, immunological markers including a cluster of differentiation emerged as a key molecular marker for cancer diagnosis. The future directive is to develop molecular makers for each class of cancer for early diagnosis. In the context of several physiological parameters, enzymes, genes and cell cycle regulatory proteins are being studied. Here, nanotechnology has played a vital role in understanding these mechanisms running at cellular and subcellular level. Further, studies are required for real time monitoring of cell cycle and progression of cancer tissue.

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AMR the Next Concern After COVID-19

- New antibiotic development cannot keep up with the rate of bacterial resistance, thus giving rise to the antimicrobial resistance (AMR) crisis. There is a smaller market size and profit incentive for pharma companies for developing new antibiotics in comparison with lifestyle medications and other therapies that have broader indications. Therefore, the number of new antibiotics approved by the FDA annually has reduced.
- While earlier it took an average of 21 years for bacteria to become resistant when antibiotics were first used, it takes just 1 year on average today to develop resistance against a drug. The CDC has listed 18 different types of antibiotic-resistant bacteria and has classified five as urgent threats to human health.
- Carbapenem-resistant Enterobacteriaceae (CRE) are one of the most concerning mutating bacteria. Mortality due to CRE infection has been estimated to be as high as 40-50%. Antibiotic-resistant bacteria in the healthcare setting, including CRE and methicillin-resistant *Staphylococcus aureus*, account for more than 85% of the antibiotic-resistant deaths, suggests the CDC analysis.
- Up to 30% of patients with severe *Clostridium difficile* colitis and sepsis need emergency surgery, and the mortality among patients undergoing surgery is high. Overuse of antibiotics is the key factor behind antibiotic resistance today.
- The CDC has stated that in 2018, seven antibiotic prescriptions were given for every 10 Americans. One-third of these were considered unnecessary, and frequently were for viral illnesses that are not responsive to antibiotics, including sinus infections, ear infections, viral sore throats and common cold. Clinicians who write such prescriptions often argue that giving the antibiotic would be of help if there is a small bacterial component involved or if the infection gives rise to an opportunity for bacterial infection.
- The overuse of antibiotics has been apparent in the treatment of COVID-19.
- A meta-analysis published in the *Journal of Clinical and Infectious Diseases*, including 18 studies that involved 2,010 hospitalized COVID-19 patients, reported that 72% of the patients got an antibiotic, despite the fact that only 8% of them had a bacterial co-infection. Azithromycin was frequently prescribed early in the pandemic as some questionable evidence suggested that the drug had an antiviral effect.
- AMR might be worsening during the ongoing pandemic. Nearly 70-80% of all antibiotics in the US are given to animals; crowded conditions aid mutations. As the animals develop drug resistance, it can spread to the environment and reach our food. It can subsequently be transferred to people who eat that food.
- Antibiotic use is also rampant in salmon farms. It is a matter of concern as 90% of fresh salmon eaten in the US comes from farms. Responding to the increasing resistance threat in the food industry, some fast food chains have moved to antibiotic-free animal products. Many fast-food chains have shown progress in limiting the use of antibiotics in chickens. The public interest group PIRG has developed a scorecard that compares antibiotic practice patterns of fast-food chains and can help guide consumers away from the companies that use antibiotics.
- In 2017, the use of antibiotics to promote growth in livestock was banned by the FDA.

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Uses of Antithyroid Antibodies in Nonvascular Hemisensory Impairment

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ABSTRACT

Aim: To find out the uses and correlation of antithyroid antibodies in patients with hemisensory impairment. **Background:** In day-to-day clinical practice, we have difficulties in managing patients with hemisensory impairment, where the diagnostic tests are not supporting clinical localization. **Material and methods:** All patients, aged 18 years and above, who came to the Neurology Department between February 2018 and August 2019 with either right or left persistent hemisensory impairment with or without facial involvement, were included. After the clinical assessment, appropriate investigations (complete blood counts, urea, creatinine, electrolytes, thyroid-stimulating hormone [TSH], serum B12, antinuclear antibodies [ANA] profile, perinuclear antineutrophil cytoplasmic antibodies [pANCA], cytoplasmic antineutrophil cytoplasmic antibodies [cANCA], neurolaboratory tests, carotid vertebral arterial Doppler study, magnetic resonance imaging [MRI] brain with magnetic resonance angiogram [MRA]/MRI brain with contrast) were done to confirm the diagnosis or to treat accordingly. Patients with acute stroke, demyelination, hemiplegic migraine and transient ischemic attack (TIA) were excluded. Rest of them were advised to undergo serum antithyroid antibodies and psychiatric assessment. Patients with positive antithyroid antibodies were treated with prednisolone 1 mg/kg/day for 6 weeks and reviewed. Psychiatric follow-up was done in patients with negative antithyroid antibody reports. Uses and correlation of antithyroid antibodies were analyzed. **Results:** A total of 33 patients were studied. Among them, 28 (85%) were females, 5 (15%) males and the mean age of presentation was 41.6 years. Out of 33 patients, 27 (82%) had subjective feeling of subacute onset persistent tingling sensation or numbness or tightness or hypo-/hyperesthesia or uneasiness on either side of the body with or without face involvement. Rest of the 6 patients (18%), had numbness with feeling weak on one side with no demonstrable sensory motor deficit. Antithyroid antibodies (antithyroglobulin and antithyroid peroxidase antibodies) were positive in 21 (64%) patients with hemisensory impairment. In this study, 28 (85%) were in euthyroid, 3 patients (9%) in hypothyroid and 2 (6%) were in hyperthyroid groups. Antithyroid antibodies were positive in 61%, 66% and 100%, respectively in the thyroid groups. None of our study patient had psychiatric illness or brain lesions on MRI study. **Conclusion:** Autoimmune thyroiditis can present with new onset persistent hemisensory impairment in young adults, which is more common in females. Both antithyroid antibodies are clinically useful in the diagnosis and management of nonvascular hemisensory impairment. Hence, the strong clinical judgment not supported by the diagnostic tests might alert the physician to rule out autoimmune thyroiditis in neuroaxis.

Keywords: Antithyroid antibodies (antithyroglobulin and antithyroid peroxidase antibody), thyroid-stimulating hormone, antinuclear antibodies profile, antineutrophil cytoplasmic antibodies, transient ischemic attacks, neuroaxis

The significance of the neurologic examination in the diagnosis of diseases of the nervous system can never be overstated. Neurologic diagnosis is often considered difficult as most parts of the nervous system cannot be examined directly, and its complex organization and integrated functions are difficult to comprehend by means of a superficial observation.[1] In day-to-day practice, we have difficulties in managing patients with hemisensory impairment, where the diagnostic tests are not supporting clinical localization. Hence, this study will help in such cases for early diagnosis and better management.

The uniqueness of this study is a rare presentation of autoimmune thyroiditis as hemisensory impairment and uses of antithyroid antibodies in such cases are discussed.

MATERIAL AND METHODS

All patients, aged 18 years and above, who came to the Neurology Department between February 2018 and

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August 2019 with either right or left persistent hemisensory impairment with or without facial involvement, were included. After the clinical assessment, appropriate investigations (complete blood counts, urea, creatinine, electrolytes, thyroid-stimulating hormone [TSH], serum B12, antinuclear antibodies [ANA] profile, perinuclear antineutrophil cytoplasmic antibodies [pANCA], cytoplasmic antineutrophil cytoplasmic antibodies [cANCA], neurolaboratory tests, carotid vertebral arterial Doppler study, magnetic resonance imaging [MRI] brain with magnetic resonance angiogram [MRA]/MRI brain with contrast) were done to confirm the diagnosis or to treat accordingly. Patients with acute stroke, demyelination, hemiplegic migraine and transient ischemic attack (TIA) were excluded. Rest of them were advised to undergo serum antithyroid antibodies and psychiatric assessment. Patients with positive antithyroid antibodies were treated with prednisolone 1 mg/kg/day for 6 weeks and reviewed. Psychiatric follow-up was done in patients with negative antithyroid antibody reports. Uses and correlation of antithyroid antibodies were analyzed.

STATISTICAL METHODS

All categorical variables expressed as percentage. The continuous variables represented as mean ± SD. Data entry was done in MS-Excel spreadsheet. Data analyses performed using Statistical Package for the Social Sciences software (SPSS 16).

RESULTS

A total of 33 patients were studied. Among them, 28 (85%) were females, 5 (15%) males and the mean age of presentation was 41.6 years. Antithyroid antibodies (antithyroglobulin and antithyroid peroxidase antibodies) were positive in 21 patients with hemisensory impairment.

Age distribution and their antithyroid antibody positive status were as below (Fig. 1).

Out of 33 patients, 27 (82%) had subjective feeling of subacute onset persistent tingling sensation or numbness or tightness or hypo-/hyperesthesia or uneasiness on either side of the body with or without face involvement. Rest of 6 patients (18%), had numbness with feeling weak on one side with no demonstrable sensory motor deficit. None of our study patient had psychiatric illness or brain lesions on MRI (including diffusion-weighted images [DWI]).

In this study, 28 (85%) were in euthyroid, 3 (9%) in hypothyroid and 2 (6%) were in hyperthyroid groups.

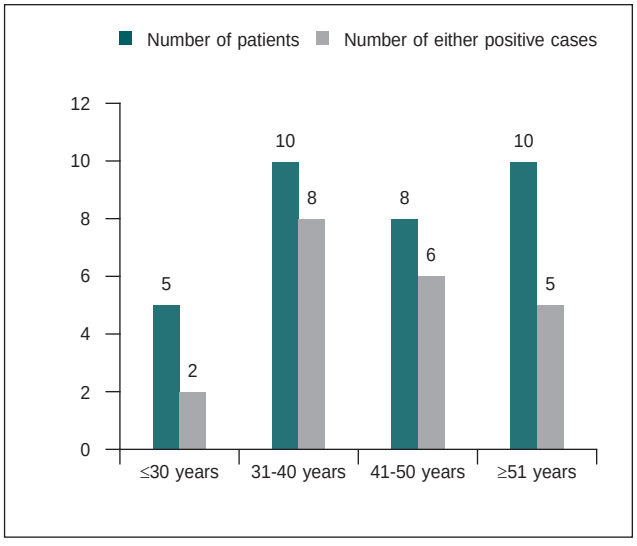

Figure 1. Age distribution of 33 patients.

Table 1. Thyroid Groups with Positive Antithyroid Antibodies

Thyroid Groups (Number of patients)	Number of antithyroid antibody positive cases (%)
Euthyroid 85% (28 patients)	17 (61%)
Hypothyroid 9% (3 patients)	2 (66%)
Hyperthyroid 6% (2 patients)	2 (100%)
Total (33 patients)	**21 (64%)**

Antithyroid antibodies were positive in 61%, 66% and 100%, respectively in the thyroid groups (Table 1).

Irrespective of the TSH level, antithyroid antibodies were positive in all three thyroid groups.

DISCUSSION

Hashimoto's thyroiditis is the most common autoimmune thyroid disease. More than adequate or excessive iodine intake may lead to autoimmune thyroiditis[2-4] by generating reactive oxygen intermediates, by increase in immunogenicity and by increasing the lymphocytic infiltration of the thyroid.[5] Neurological manifestations of Hashimoto's thyroiditis include generalized/focal seizures, status epilepticus, myoclonus, stroke, hyperreflexia, tremors, encephalopathy and psychiatric manifestations such as psychosis, visual hallucination, paranoid delusion, mania, depression, dementia and catatonia.[6,7]

In our study, 33 patients with hemisensory impairment, majority 28 (85%) were females and mean age of presentation was 41.6 years. Out of 33 patients, 27 (82%)

had subjective feeling of subacute onset persistent tingling sensation or numbness or tightness or hypo-/hyperesthesia or uneasiness on either side of the body with or without face involvement. Rest of the 6 patients (18%), had numbness with feeling weak on one side with no demonstrable sensory motor deficits. Basic neurology teaching is, deficits in a hemi-distribution suggest either the cortex, subcortex or thalamic lesion. Crossed deficits, affecting the face on one side and the body on the opposite side, suggest brainstem disease. But none of the 33 patients had brain lesions in MRI, including DWI.

Irrespective to their thyroid status, 21 patients with positive antithyroid antibodies had dramatic response to oral steroids. Mechanism of antithyroid antibodies causing sensory deficits is not known.

The formation of autoantibodies against the thyroid gland, cross-reacts with the N-terminal of endothelial α-enolase (NAE). This may cause autoimmune vasculitic infarct, the possible mechanism causing the vasculitic type of Hashimoto's encephalopathy, but none of our study patient had encephalopathy. This is a new observation in association of antithyroid antibodies with nonvascular hemisensory impairment. In future, we have a plan of doing positron emission tomography (PET) scan to know the metabolic abnormalities in patients with hemisensory impairment.

As per Toth et al, in a study on 34 patients with hemisensory syndrome, 6 patients (17.5%) had psychiatric illness.[8] However, no psychiatric illness was identified among the 33 patients in our study. Hence, autoimmune thyroiditis can present with persistent hemisensory impairment in neuroaxis. The strong clinical judgment not supported by the diagnostic tests might alert the physician to rule out autoimmune thyroiditis in neurology. In future, large samples including control groups will address the significance of this observational study.

CONCLUSION

Autoimmune thyroiditis can present with new onset persistent hemisensory impairment in young adults which is more common in females. Both antithyroid antibodies are clinically useful in the diagnosis and management of nonvascular hemisensory impairment. Hence, the strong clinical judgment not supported by the diagnostic tests might alert the physician to rule out autoimmune thyroiditis in the neuroaxis. In India, iodine supplementation should be targeted at iodine-deficient areas in order to reduce the prevalence of thyroid autoimmunity.

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Indian Journal of Clinical Practice, Vol. 31, No. 9, February 2021

To Study the Efficacy and Safety of a Polyherbal Formulation in Nonalcoholic Fatty Liver Disease Patients

PRAVIN RATHI*, PRABHA SAWANT†, DIPESH WAGHMARE‡

ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is a global health problem with no effective therapeutic treatment. The term NAFLD is used to describe a wide spectrum of fatty liver changes ranging from fatty liver and steatosis on one side to nonalcoholic steatohepatitis (NASH) and cirrhosis on the other. The pathogenesis of NAFLD has not been fully elucidated which makes its treatment difficult using a single pharmacological drug. In Ayurveda, the Indian traditional system of medicine, the use of herb extracts or polyherbal formulations to treat various liver diseases has been mentioned. A polyherbal formulation has been shown to be effective in the treatment of patients with NAFLD. **Objective:** The purpose of this study is to investigate the efficacy and safety of a polyherbal formulation on hepatic fat content as well as biochemical and anthropometric features of patients with NAFLD. Therefore, we undertook this randomized, double-blind, parallel-group and placebo-controlled clinical trial in patients diagnosed with NAFLD. **Methods:** All adult patients meeting the inclusion criteria were included in the study. Patients diagnosed with fatty liver disease including NAFLD were treated for 6 months with two capsules twice a day of either a polyherbal formulation or placebo as per randomization. Patients were asked to take the fat-free diet as far as possible but no standard diet was recommended. Liver function test (LFT), lipid profile, the fat content of liver as measured by ultrasonography (USG) and magnetic resonance imaging (MRI) were assessed on Day 0, after 3, 6 and 9 months as efficacy parameters. Complete blood count (CBC) and renal function tests (RFTs) were assessed as safety parameters. Global assessment of treatment was also recorded at the end of the study. **Results:** Compared with placebo, the polyherbal formulation led to a significant reduction in liver fat content (48.13% improvement in the polyherbal formulation group vs. 20.95% improvement in the placebo group). There were significant reductions in body mass index and ALT, AST, ALP, serum bilirubin levels compared with the placebo group. All these reductions were highly significant ($p < 0.001$). However, there was no significant change in lipid profile and liver volume. **Conclusion:** The polyherbal formulation is a very effective and safe treatment option in patients with nonalcoholic fatty liver. It significantly improves the liver function and reduces lipid content of the liver as compared to placebo.

Keywords: Fatty liver disease, nonalcoholic fatty liver disease, herbal product

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of vesicles of fat (mainly triglycerides) in the hepatocytes in the absence of classic causes of steatosis, with alcohol being one of the most frequent of these causes.[1] NAFLD is closely related to overweight, disturbed glucose homeostasis and metabolic syndrome (although it can also be present in patients without any features of metabolic syndrome, often referred to as "lean nonalcoholic steatohepatitis [NASH]").[2,3]

While the current definition limits NAFLD to a diagnosis of exclusion, it must be understood that NAFLD can co-exist with other chronic liver diseases, which often leads to synergistic effects in terms of disease progression. NAFLD includes a spectrum of liver disease. Steatosis may be the only lesion characterizing nonalcoholic fatty liver (NAFL). However, steatosis can also be associated with chronic low-grade inflammation and hepatocellular damage.[1] NAFLD can be associated

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with progressive fibrosis and can lead to liver cirrhosis with decompensation and/or the development of hepatocellular carcinoma (HCC). The natural history of NAFLD is not clearly understood. The estimated prevalence of NAFLD is 25-30% in the Western adult population, mainly based on noninvasive tests such as liver enzymes or ultrasound, with higher prevalence in populations with risk factors like obesity or diabetes.[4]

Pathophysiology of NAFLD remains unclear. A better understanding of the pathophysiology would help understand potential therapies. Patients with NAFLD often remain asymptomatic. Most of them thus remain undiagnosed for several years until they progress to advanced fibrosis or cirrhosis and HCC. Patients may sometimes develop vague right upper quadrant pain, hepatomegaly and may have normal or high alanine aminotransferase (ALT) and usually have risk factors for metabolic syndrome. About 70-80% of people with NAFLD have insulin resistance or metabolic syndrome.[5] There is no definite pharmacotherapy for NAFLD as yet. Benefits have been seen with lifestyle modification with regular exercise and dietary changes or bariatric surgery in morbidly obese patients, resulting in gradual weight loss.[6-8] As pathophysiology is complex and with heterogeneous patient population and difficulty in diagnosis and therapy monitoring, drug development poses challenges. Some drugs currently approved for other indications seem effective and can be used, but new treatments are eagerly awaited.

Under these circumstances, alternative systems of medicine may provide some solution. In Ayurveda, the Indian traditional system of medicine, several herbs have been described to be used for the treatment of fatty liver disorders. A polyherbal formulation developed using a judicious combination of such herbs for the treatment of liver disorders has been tested. Many of the plants used in this preparation have been shown to have very good hepatoprotective, anti-inflammatory and antioxidant activities in several animal models. This manuscript highlights the current evidence on pharmacological and nonpharmacological therapeutic options for NAFLD.

OBJECTIVE

The purpose of this study is to investigate the efficacy and safety of a polyherbal formulation on hepatic fat content as well as biochemical and anthropometric features of patients with NAFLD. We undertook this randomized, double-blind, parallel-group and placebo-controlled clinical trial on patients diagnosed with NAFLD.

MATERIAL AND METHODS

This was a double-blind, randomized, multicentric, parallel-group and placebo-controlled clinical trial conducted on patients diagnosed with fatty liver disease including NAFLD. The inclusion criteria were males and females aged 18 years or above diagnosed with fatty liver disease because of any etiology. NAFLD was defined as a raised serum ALT or aspartate aminotransferase (AST) (ALT >41 IU/L or AST >34 IU/L) during the screening period. The patients also had to have abnormal levels of biochemical markers for more than 6 months, with a body mass index (BMI) higher than 25 and signs of hepatic steatosis diagnosed by ultrasonography (USG) and magnetic resonance imaging (MRI).

Patients with decompensated diabetes mellitus, high cholesterol and triglycerides, diagnosis of hepatitis B and C, patient drinking more than 40 g ethanol/week and those with other concomitant hepatic or recognized systemic disease were excluded from the study. Eligible subjects were randomly assigned to receive a polyherbal formulation (n = 30) or placebo (n = 30) two capsules twice daily for 6 months. The contents of the polyherbal formulation are Bhuiamla (*Phyllanthus amarus*), Amla (*Emblica officinalis*), Haritaki (*Terminalia chebula*), Bibhitaki (*Terminalia bellirica*), Bhringraj (*Eclipta alba*), Pittapapda (*Fumaria parviflora*), Chitrakmool (*Plumbago zeylanica*), Kalmegh (*Andrographis paniculata*), Kutki (*Picrorhiza kurroa*), Soonth (*Zingiber officinale*), Pippali (*Piper longum*), Punarnava (*Boerhavia diffusa*).

The primary efficacy variables included liver function test (LFT), lipid profile, the fat content of liver measured by USG and MRI and secondary efficacy parameters included changes in BMI, body weight and global assessment by the physician and also by the patient. Safety variables included complete blood count (CBC), renal function test (RFT) and adverse effects. Vital signs, laboratory investigations (LFTs, lipid profile), the fat content of liver measured by USG and MRI were assessed on Day 0, after 3, 6 and 9 months as efficacy parameters. CBC and RFT were assessed as safety parameters. Global assessment of treatment was also recorded at the end of the study. All illnesses (apart from fatty liver disease), which occurred during the course of the study, were documented as intercurrent illness and the same was done for adverse events along with the medication for the same.

Efficacy assessment was done on patients completing the study period, whereas safety analysis was done on all patients receiving the study drug. Statistical analyses were performed using the SPSS software

version 10.0. Descriptive statistics were given as mean ± SD (n = 30) for numerical variables. Student's paired test (parametric) and Wilcoxon signed-rank test (nonparametric) were applied to compare between two related groups. Student's unpaired *t*-test (parametric) and Mann-Whitney U test (nonparametric) were applied to compare between two unrelated groups. All the statistical tests were two-tailed. The level of significance was taken as p = 0.05.

RESULTS

All the 60 patients recruited in the study completed 6 months treatment and 3 months follow-up (total study duration was of 9 months). There were no dropouts or lost to follow-up. The patients in both groups were matching demographically. The demographic details of the patients are shown in Table 1.

Assessment of Primary Efficacy

A significant improvement was seen in the efficacy parameters with the polyherbal formulation. ALT levels in the polyherbal treated group reduced from an initial value of 102 ± 22 IU/L to 40 ± 18 IU/L, a reduction of 60.8% after 6 months and to 36 ± 20, reduction of 64.7%, after 9 months. Similar results were seen with AST with 57.1% and 58.6% reduction, and alkaline phosphatase (ALP) with 65.2% and 66.7% reduction (Fig. 1), as well as in total bilirubin with 52.6% and 52.6% reduction (Fig. 2) after 6 and 9 months, respectively. All these reductions were highly significant ($p < 0.001$) in comparison with the placebo group. The polyherbal formulation and placebo did not show any significant reduction in lipid profile (Figs. 3 and 4).

There was a significant reduction in the fat content of the liver in the polyherbal treated group as observed in USG in comparison to the placebo group. MRI results revealed that the fat content in liver of polyherbal treated group before treatment was 45.5 ± 27.9 (mean ± SD) which reduced to 23.6 ± 12.0 at the end of 9 months, a total reduction of 48.13% which was highly significant ($p < 0.001$) in comparison with the placebo group (Fig. 5), while no group showed any significant

Table 1. Demographic Details

Parameters	Polyherbal product	Placebo
No. of patients	30	30
Male	25	26
Female	5	4
Weight (kg)	88.0 ± 11	84.0 ± 15

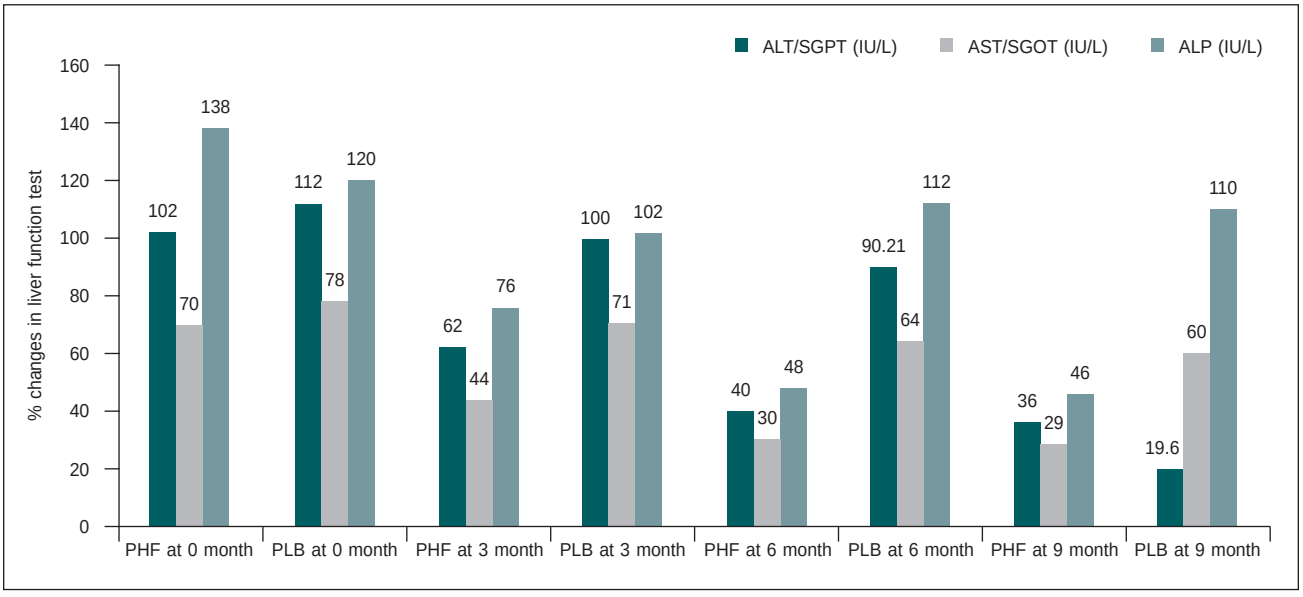

Figure 1. Improvement was seen in liver function test.

PHF = Polyherbal formulation; PLB = Placebo; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase.

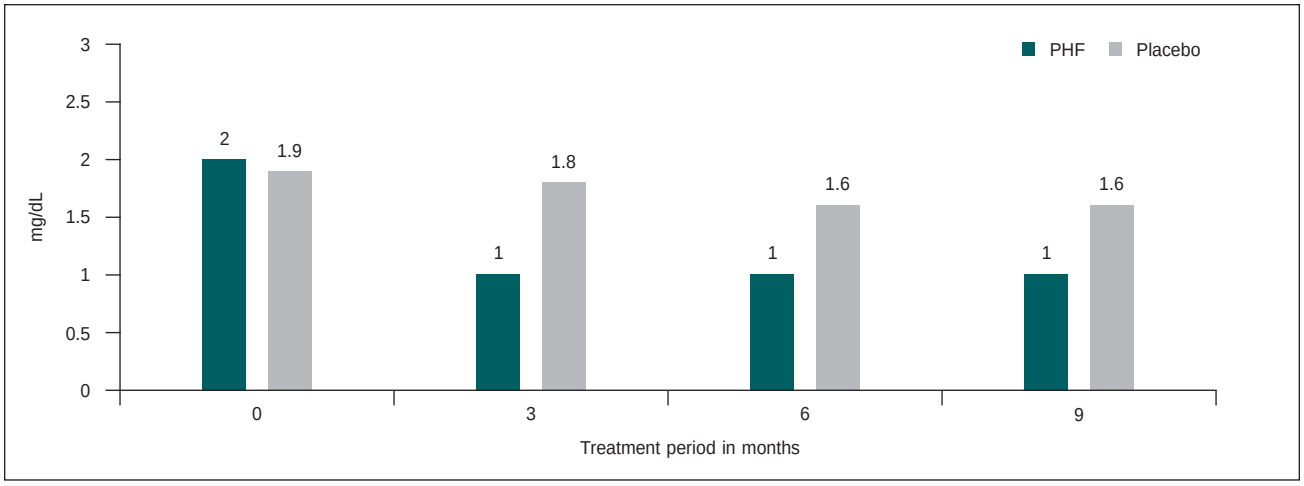

Figure 2. Effect of polyherbal formulation on serum bilirubin.

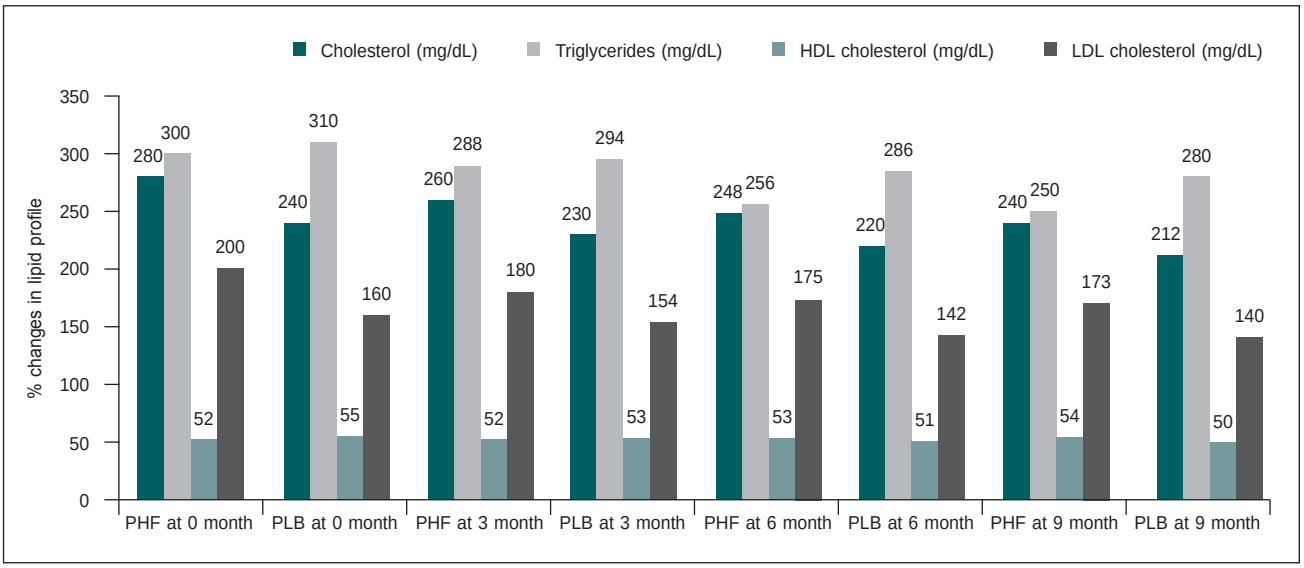

Figure 3. Effect of polyherbal formulation on lipid profile (mean ± SD).

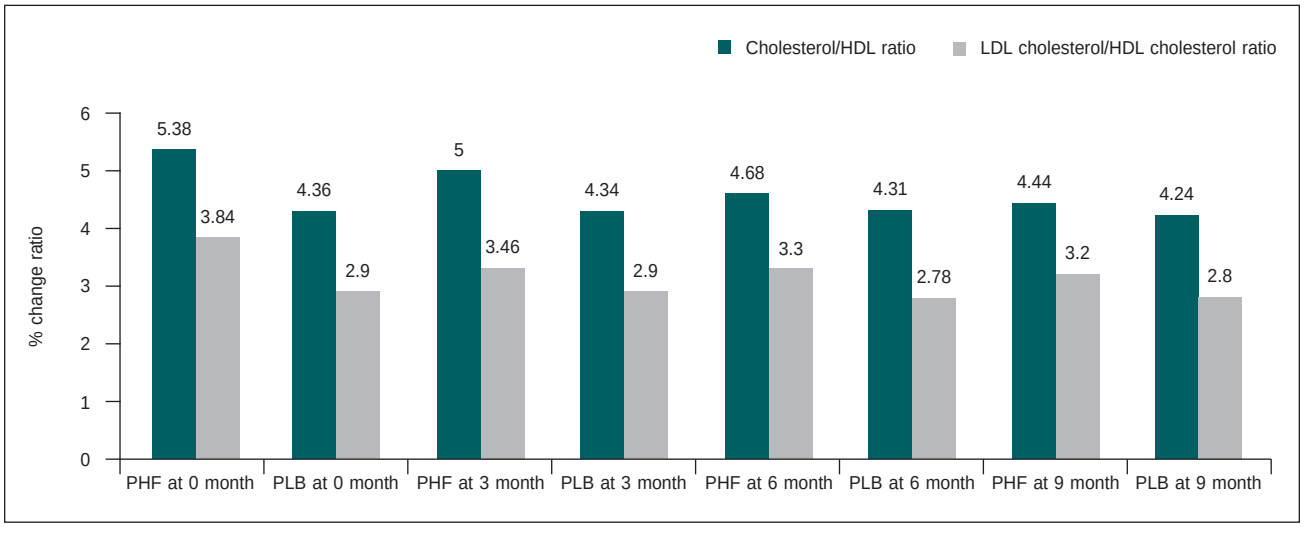

Figure 4. Effect of polyherbal formulation on HDL and LDL cholesterol ratio.

changes in liver volume. The liver volume of polyherbal treated group reduced from 2255 ± 530 cc to 1948 ± 261 (13.6%) after 6 months and to 1944 ± 320 (13.8%) after 9 months, but this was not significant. The placebo group also did not show any significant changes in liver volume (Fig. 6). In terms of anthropometric changes, the polyherbal formulation produced a significant change in body weight. The mean weight reduced from 88 to 83 kg after 6 months of treatment and further reduced to 81 kg after 9 months. It was significant ($p < 0.05$). Proportionately, there was a significant reduction in BMI ($p < 0.05$). No significant changes were seen in the placebo group. After 6 months of treatment, no serious adverse events were reported either in the polyherbal treated group or in the placebo group. About 5 patients in polyherbal group and 2 in the placebo group had reported some uneasy feeling with mild nausea lasting for a few minutes on first 2 days of treatment, after which no such symptoms were reported.

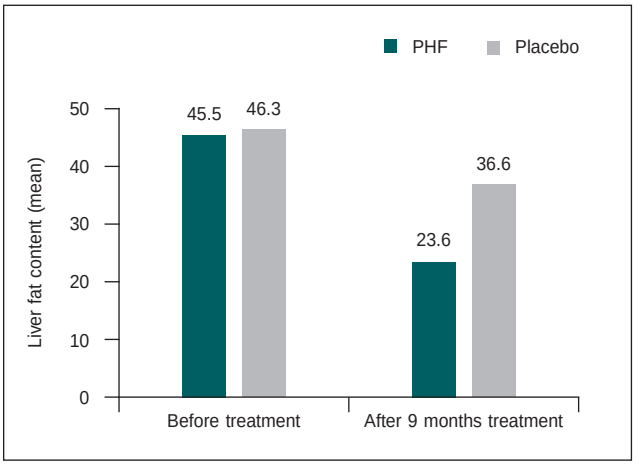

Figure 5. Effect of polyherbal formulation on the fat content of the liver as measured by MRI.

Global Assessment of Efficacy

About 70% of patients treated with the polyherbal formulation said it is good and the remaining 30% said it is fair, but none of them said it is poor. The physicians' opinion about efficacy was almost same, while in placebo group about 3% said it is good, 10% said it is fair and 87% said it is poor (Fig. 7).

Global Assessment of Safety

Majority of the patients treated with the polyherbal formulation said that the drug is safe. About 70% of

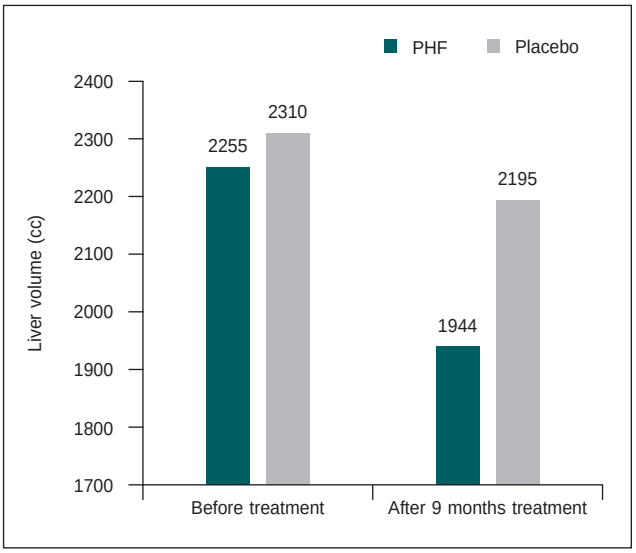

Figure 6. Effect of polyherbal formulation on liver volume (cc).

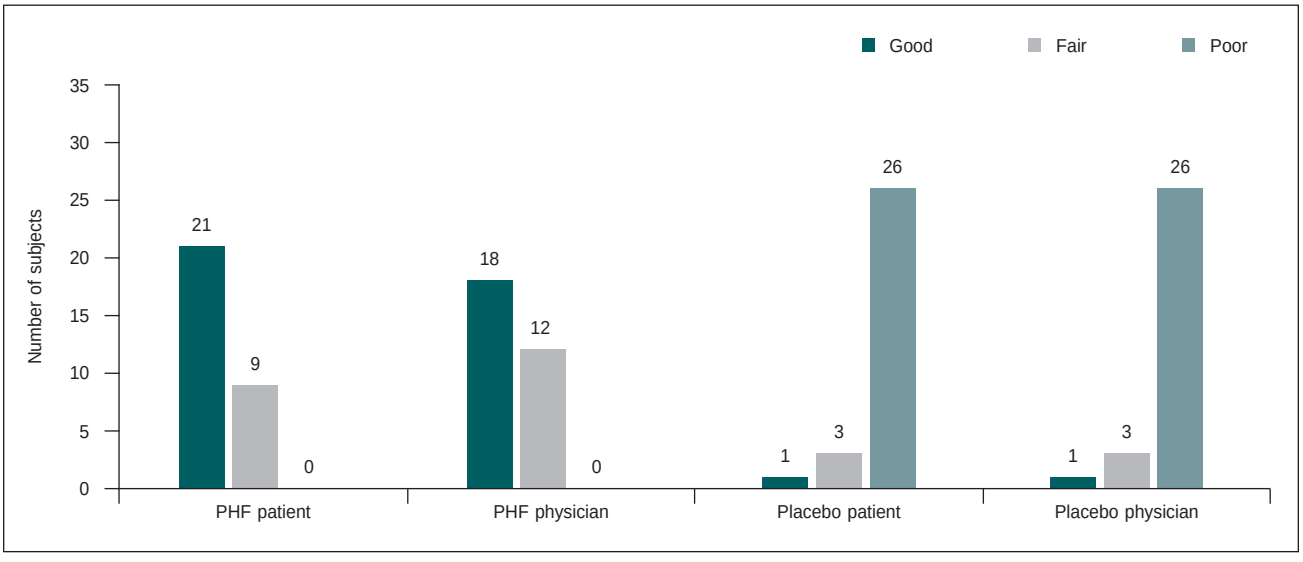

Figure 7. Global assessment of efficacy.

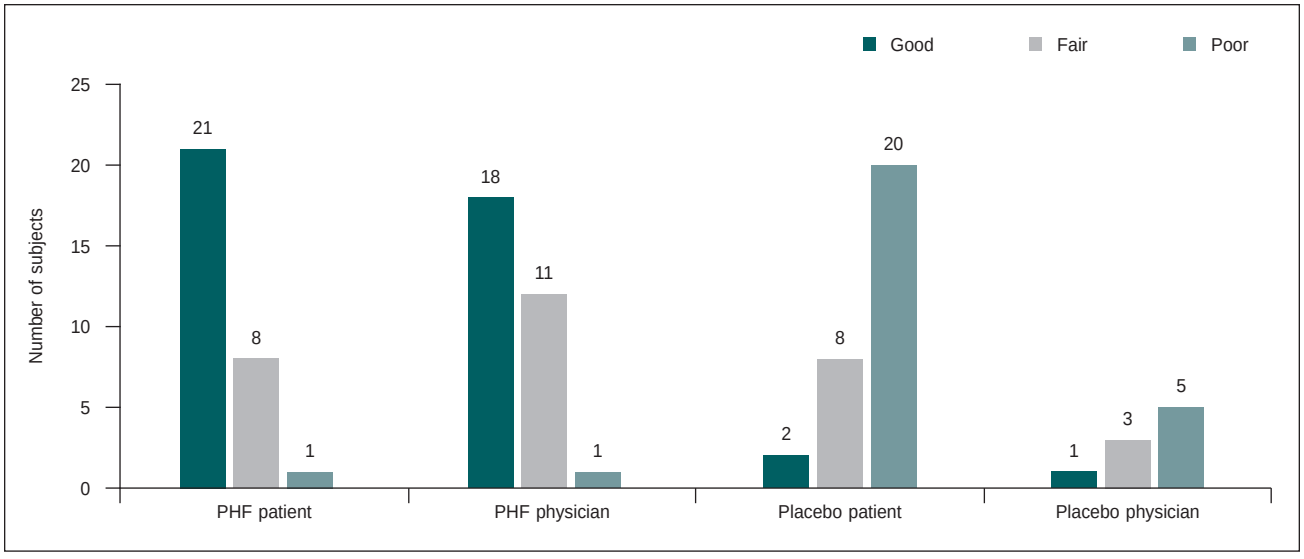

Figure 8. Global assessment of safety.

patients said it is good, 27% said it is fair and the 3% said it is poor. Physicians also had a similar opinion about its safety. In the placebo group, 6.7% said it is good, 26.7% said it is fair and 66.7% said it is poor. Physicians also had a similar opinion (Fig. 8).

DISCUSSION

Nonalcoholic fatty liver disease has now become a global health challenge. Obesity and diabetes mellitus are often associated with insulin dysregulation of glucose and lipid metabolism. The hepatotoxic fatty acids, in the setting of hyperinsulinemia, can lead to NAFLD. There is hepatic necrosis and enhanced fibrogenesis. Starting from simple steatosis, NAFLD can advance to steatohepatitis and fibrosis. The terminal complications include cirrhosis and/or hepatic carcinoma.[9] Natural active ingredients from herbs are of major pharmaceutical and therapeutic importance, deviating from standard rules of modern medicines, where instead of a single isolated fraction, a group of naturally occurring components that exert the desired therapeutic effect are used. The polyherbal capsule used in this study is one such formulation. Patients recruited in the clinical study had very high levels of ALT, AST, ALP and bilirubin suggesting that these patients had liver disorder. Further, USG showed that these patients had high-fat content in the liver which was also quantitated by MRI, suggesting a fatty liver. Since none of the patients was alcoholic, these patients can be classified as patients with NAFLD.

Treatment with the polyherbal formulation for 6 months significantly ($p < 0.001$) reduced the levels of liver enzymes. It indicates that the formulation is very effective in improving liver functions. Since this is a poly-ingredient formulation, its mode of action cannot be attributed to anyone ingredient but it is the collective action of all of the ingredients. In the Indian system of medicine (Ayurveda), all the ingredients present in this formulation have been shown to have hepatoprotective activity. Some of them have antioxidant, antimicrobial, anti-inflammatory and hypolipidemic activities too.

All the findings of the clinical study discussed above have shown that all the ingredients of this formulation are protective for the liver and support liver detoxification pathway. The formulation also possesses pharmacological activities like antimicrobial, antiviral, antioxidant, anti-inflammatory and fibrotic and anticancer properties. This formulation significantly reduces the total fat content of the liver as measured by USG and MRI and normalizes raised level of ALT, AST, ALP and serum bilirubin. This indicates that it is effective in reducing the fatty content of the liver and improving liver function.

None of the patients treated with the polyherbal formulation reported any adverse event. The formulation did not show any significant changes in hemogram and RFTs, thus suggesting that the drug is safe. Majority of the patients and the principal investigator were satisfied with treatment with the polyherbal formulation in a patient with NAFLD.

CONCLUSION

A polyherbal phytoactive formulation has proven its effectiveness and efficiency in the treatment of NAFLD

patients. Histological and laboratory findings have shown significant improvement and the liver damage has been ameliorated as compared to placebo treatment. No adverse events were reported, either clinical or investigational, indicating that the formulation is very safe. This is a promising treatment in NAFLD patients as it improves the liver functions and reduces hepatic fat storage.

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■■■■

FaST Audit Shows that Preoperative Fasting is Usually Prolonged in Patients Undergoing Surgery

A traditionally followed practice prior to elective surgery is to keep the patient fasting for around 12-24 hours. This is done to avoid the risk of vomiting and pulmonary aspiration during induction of anesthesia. Prolonged fasting significantly increases patient discomfort, thirst and hunger. It may cause dehydration and acute kidney injury, especially in the older adults, with poor postoperative outcomes. Hence, new guidelines now advocate fast for 2 hours from clear fluids and 6 hours from food for patients undergoing elective surgical procedures.

A multicenter prospective audit was conducted over 2 months to assess preoperative fasting and surgical timing (FaST) in 343 patients undergoing elective and emergency general surgery in the East Midlands region of the United Kingdom. Adherence to guidelines for fasting in patients was also examined. Of the 343 participants, 172 (50%) were males; 266 (78%) underwent elective surgery and 77 participants (22%) had emergency surgery. The median fasting time for clear fluids was 5.8 hours, while it was 16.1 hours for food. Seventy-one (21%) and 250 (73%) participants fasted for more than 12 hours for clear fluids and food, respectively. Most patients undergoing elective surgery fasted for more than 4 hours from clear fluids and more than 12 hours from food. The fasting period was even longer in patients undergoing emergency surgery; more than 12 hours from clear fluids and more than 24 hours from food. The study demonstrated poor compliance with fasting guidelines. Patients undergoing surgery tended to fast from clear fluids and food for longer durations despite guidelines recommending against prolonged preoperative fasting. The authors suggest that the available data on operative times and theatre efficiency can be used to better plan preoperative fasting in emergency as well as elective surgeries. Explaining the rationale of guidelines to patients and making them part of shared decision making may increase compliance with better outcomes of surgery.

Source: El-Sharkawy AM, et al. Clin Nutr. 2020 Sep 5:S0261-5614(20)30449-0.

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Epidemiological and Radiological Profile of Drug Sensitive TB Patients Remaining Sputum AFB Smear Positive After 2 Months of ATT

SUMIT KHATRI*, SONIA BHARTY, SANJAY BHARTY, AVINASH JAIN

ABSTRACT

Tuberculosis (TB) continues to be a major cause of morbidity and mortality. Treatment of TB has long-course and in some patients, delaying of sputum conversion has been observed. Hence, this study was conducted in 74 patients with TB who were on antituberculosis treatment (ATT) and sputum acid-fast bacilli (AFB) positive after 2 months of ATT. Out of 74 patients, 32 (43.2%) were severely thin and 70 (94%) patients had cavities in their chest X-ray.

Keywords: Tuberculosis, antituberculosis treatment, sputum AFB

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and less commonly by other organisms of the Mycobacterium complex. The disease continues to be a major cause of morbidity and mortality. India bears nearly 30% of the global TB burden. Each year, 8.74 million people develop TB and nearly 2 million die. There were about 3.8 million bacteriologically positive TB cases in the country in the year 2000.

TB is the commonest opportunistic infection occurring among human immunodeficiency virus (HIV)-positive persons in India and it is estimated that 60-70% of HIV-positive persons will develop TB in their lifetime. The directly observed treatment short-course (DOTS) strategy of the Revised National TB Control Programme (RNTCP) prescribes treatment for new smear positive patients, who have never taken antituberculosis treatment (ATT) or have taken antituberculosis therapy for less than 1 month. According to the RNTCP status report, among the 5,53,116 patients registered for treatment under category I, the cure rate was 83.8%, the default rate 6.4% and the failure rate was 2.3%. Hence, this study is required to observe epidemiological features of patients having positive sputum smear for acid-fast bacilli (AFB) after 2 months of treatment.

MATERIAL AND METHODS

An observational study was conducted on a total of 74 patients who had a diagnosis of TB and were taking anti-TB drugs under DOTS. The study was conducted at Lala Ram Sarup (LRS) Institute of Tuberculosis and Respiratory Diseases located on Sri Aurobindo Marg in South Delhi over period of 1 year. The study group consisted of patients who were sputum smear-positive for AFB after 2-month of treatment regimen under DOTS.

On the first visit, patients were interviewed on their clinical and treatment histories. For all patients, informed consent was taken in either English or Hindi. The patients' physical characteristics, like height and body weight, were noted and the body mass index (BMI) was calculated and history of diabetes mellitus, was assessed. The patients were subjected to HIV testing with pre-test and post-test counseling. Patients were subjected to undergo chest X-rays.

The chest X-rays were classified as follows:

- **Minimal:** Minimal lesions include those that are of slight to moderate density but do not contain demonstrable cavitation. They may involve a small part of one or both the lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side that occupies the space above the second

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chondrosternal junction and the spine of the fourth or body of the fifth vertebra.

- **Moderately advanced:** Moderately advanced lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density that may extend throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third the volume of one lung; total diameter of cavitation, if present, must be less than 4 cm.
- **Far advanced:** Lesions more extensive than moderately advanced. For the purpose of simplicity and ease of analysis, minimal and moderately advanced radiological diseases were clubbed together under "less extensive" disease and far advanced radiological disease was classified as "more extensive" disease.

RESULTS

The study was conducted among the patients attending the DOTS centers coming under the purview of LRS Institute of Tuberculosis and Respiratory Diseases. The study group consisted of patients who were sputum smear-positive for AFB after 2-month of category I treatment under DOTS. The baseline characteristics of the patients are mentioned in Table 1.

Table 1. Baseline Characteristics

Epidemiological data	No. of patients	Percentage (%)
Age (years; mean - 34.7)		
Gender		
Male	53	71.6
Female	21	28.4
BMI (kg/m^2; mean - 16.83)		
History of diabetes	6	8.1
HIV status	2	2.7
Radiological features		
Far advanced	58	78.4
Less advanced	16	21.6
Cavity in chest X-ray	70	94.6
Initial sputum grading	53	71.6
3+	21	28.4
Non 3+		

Age and Sex Distribution

The study population consisted of 53 (71.6%) males and 21 (28.4%) females (Table 2). The age of the patients in the study group ranged from 15 to 75 years with a mean of 34.65 years. Fifty-six (75.67%) patients in the study group belonged to the age group of 15-45 years and 18 (24.32%) were in the age group of 46-75 years (Table 3 and Fig. 1).

BMI of Patients

The body mass index (BMI) of patients from the case group ranged from 10.40 to 27.63 kg/m^2 with a mean (±SD) of 16.83 ± 3.39 kg/m^2. According to World Health Organization (WHO) classification, 32 (43.2%) patients from the case group were severely thin (Table 4 and Fig. 2).

When low BMI was further analyzed, it was found that BMI of 32 (43.2%) patients was below 16 kg/m^2 from study group (Table 5).

Chest X-ray Profile

All X-rays were reviewed by us and 70 (94.6%) patients among the study group showed the presence

Table 2. Sex Distribution

Patient groups	Gender	
	Male	Female
Cases (n = 74)	53 (71.6%)	21 (28.4%)

Table 3. Age Distribution

	Age in years		
	15-45	46-65	>65
No. (%) of patients	56 (75.67)	16 (21.62)	2 (2.71)

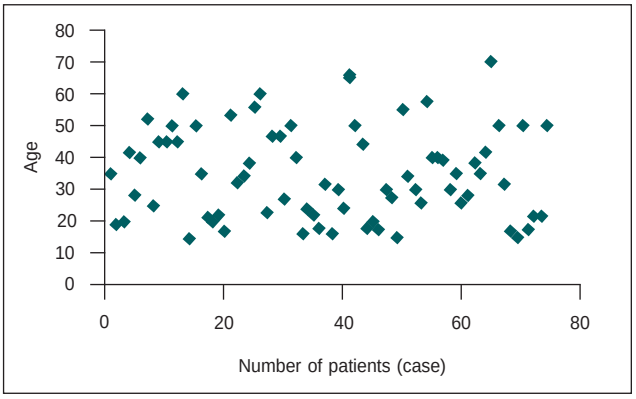

Figure 1. Age distribution.

Table 4. BMI of Patients

BMI type according to WHO classification	Case (%)
Mild thinness	6 (8.1)
Moderate thinness	12 (16.2)
Severe thinness	32 (43.2)
Pre-obese	2 (2.7)
Normal weight	22 (29.7)

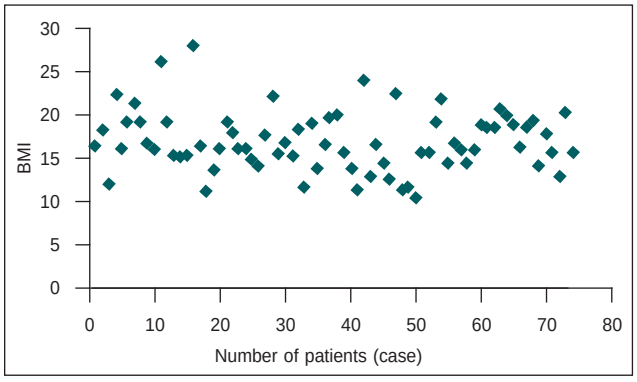

Figure 2. BMI of patients.

Table 5. BMI of Patients

BMI cut-off 16	Case (%)
BMI <15.99	32 (43.2)
BMI ≥16	42 (56.8)

Table 6. No. of Patients with Cavity in Chest X-ray

Cavity	Case (%)
Yes	70 (94.6)
No	4 (5.4)

Table 7. No. of Cavities in Chest X-ray

Cavity number	Case (%)
No cavity	4 (5.4)
Single	9 (12.2)
Multiple	61 (82.4)

of cavitating disease. The remaining 4 (5.4%) cases showed no cavity (Table 6). The X-rays which showed the presence of cavity were further divided on the basis of having single or multiple cavities. In the study group, 9 (12.2 %) and 61 (82.4%) had single and multiple cavities, respectively (Table 7). Thus, presence of cavitating disease was associated with sputum smear positivity after 2 months of treatment.

Table 8. No. of Patients and Extent of their Disease on Chest X-ray

	Extent of disease	
	Less advanced	Far advanced
Cases (n = 74)	16 (21.6%)	58 (78.4%)

Extent of Disease

Among the 74 patients in the study group, 16 (21.6%) had less extensive disease and 58 (78.4%) had more extensive disease (Table 8). It was seen that more extensive disease on chest X-ray was associated sputum smear positivity after 2-month of treatment.

DISCUSSION

The aim of this study was to profile the patients who were sputum smear AFB positive after 2-month of treatment regimen under DOTS.

The mean age of patients in the study group was 34.65 years and ranged from 15 to 75 years. Gupta et al also found mean age of TB patients to be 35.56 years. In our study, 53 (71.6%) cases were male and 21 (28.4%) cases were female. This is in accordance with the epidemiological findings that TB is more common among men and it usually affects people in the age group of 15-45 years, and hence, has severe economic implications for the country as a whole.

There were 6 patients of diabetes mellitus among the patients in the case group and among the control group. But, there was no significant difference in the outcome of the treatment between diabetes group and nondiabetes group. Two patients from the case group turned out to be positive for HIV. All HIV-positive patients were cured on treatment. Singla et al found in a study that the association of diabetes did not affect the final treatment outcome among pulmonary TB patients. Banu Rekha et al noted that at the end of intensive phase, the smear conversion rate in pulmonary TB, TB with type 2 diabetes mellitus (DM-TB) and HIV-TB groups were similar. Balasubramanian et al found 94% cure rate in diabetic patients despite poor glycemic control. Swaminathan et al found in a study that smear and culture conversion rates at 2 months were 70% and 91%, respectively in HIV-positive patients, indicating good initial response to the intermittent short-course regimens used.

On classifying BMI according to WHO classification, 32 (43.2%) patients in case group were severely thin. This

shows BMI does have a bad effect on persistent sputum smear positivity and treatment outcome. A study found that low BMI was associated with poor outcome. It also found that severe malnutrition was associated with poorer outcome as compared to mild malnutrition. Chheng et al found low BMI as a predictor of pulmonary TB with P value of <0.001. Santha et al found higher death rates to have an independent association with weight <35 kg (adjusted odds ratio [AOR] 3.8; 95% confidence interval [CI] 1.9-7.8) among TB patients.

Radiologically advanced disease in the form of cavitating disease and more extensive involvement of the lungs was observed to be associated with a persistent sputum smear positivity and poor outcome. Singla et al also had the same observation in their study and they had concluded that cavitating disease on the chest X-ray was a harbinger of poor treatment outcome.

CONCLUSION

This study concluded that low BMI, radiologically extensive disease and presence of cavitation delays sputum conversion.

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The Usefulness of Ultrasound Guidance in Fresh Embryo Transfers: A Retrospective Study

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ABSTRACT

Objective: To evaluate retrospectively the efficacy of ultrasound-guided embryo transfer method on pregnancy and implantation rate and compare with clinical touch method. **Material and methods:** The results of 582 cycles from our *in vitro* fertilization and embryo transfer (IVF-ET) program conducted at Jaipur Fertility Centre, an Infertility Unit of Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan were analyzed retrospectively and comparison was made between those carried out using ultrasound guidance and those by clinical touch method. **Results:** Higher pregnancy and implantation rates (37.19% and 19.66%, respectively) were found in the group using the transabdominal ultrasound guidance during ET compared with those in the group using the clinical touch method (30.92% and 16.22%, respectively). The difference was not statistically significant. **Conclusion:** Older women (>35 years) and in the subgroup when the clinician rated the transfer procedure as easy with some difficulty, there appeared to be a substantial improvement in the pregnancy rate and the difference was statistically significant. We believe that ultrasound-guided ET should be used in these subgroups.

Keywords: Clinical touch, embryo transfer, *in vitro* fertilization, retrospective study, ultrasound-guided, air bubble

Transabdominal ultrasound-guided embryo transfer (ET) has been described by various authors since 1985 to improve the pregnancy rate.[1-4] However, significantly higher pregnancy rates following transabdominal ultrasound guidance have not been consistently demonstrated. Lindheim et al, first reported that ultrasound guidance improved pregnancy outcome only in easy transfer.[5] Subsequently, two studies demonstrated significant differences between the clinical touch method and transabdominal ultrasound-guided ET retrospectively[6] and prospectively.[7]

Most studies trying to address the issue of whether ultrasound guidance is beneficial to ET conclude that although pregnancy rates may not be significantly raised, ultrasound guidance provides both the clinicians and patients with greater degree of confidence in the ET procedure.[3,4,8] We divided our study population according to: i) Number of embryo transferred; ii) age of patient; and iii) ease of transfer to delineate a subgroup of patients that would particularly benefit from their embryo being transferred under ultrasound guidance.

MATERIAL AND METHODS

A retrospective study of *in vitro* fertilization and embryo transfer (IVF-ET) cycles from June 2011 to August 2012 was performed. Between June 2011 to December 2011 the clinical touch method had been adopted for 262 cycles in our IVF-ET program. Between January 2012 and August 2012, 320 cycles of IVF-ET were performed under transabdominal ultrasound guidance. During both periods, there was no change in ovarian stimulation method, oocyte retrieval, culture media and culture system. For ET, Wallace and Cook echo tip catheters were used. Exclusion criteria were: age 45-year-old, more than three previous assisted conception cycles and transfer requiring general anesthesia for the patients. One clinician and three ultrasonographers were involved in the study. All ultrasonographers were specialists in infertility. An ultrasound machine with 3.75 MHz transabdominal probe was used on all women in ultrasound group.

Controlled ovarian hyperstimulation (COH) was carried out in more than 85% of patients with

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recombinant follicle-stimulating hormone (FSH) and human menopausal gonadotropin (hMG) with half-dose of gonadotrophin-releasing hormone (GnRH) agonist after down regulation with GnRH agonist in the preceding late luteal phase. Rest of the patients were induced by short protocol with GnRH agonist along with recombinant FSH or hMG. Follicular growth was followed by transvaginal ultrasonography and once adequate follicular maturation was obtained, human chorionic gonadotropin (hCG) was administered and oocyte retrieval was performed about 36 hours later under transvaginal sonographic guidance and general anesthesia. ET was carried out on Day 3 or Day 5 after oocyte retrieval. Frozen ETs were excluded from the study.

THE EMBRYO TRANSFER PROCEDURE

We carried out all the ET in the operation theater. Three embryos were usually prepared for transfer. In case, where numbers of embryos formed were less than three, less number of embryos, i.e., one or two were transferred. The patients arrived with semi-filled bladder in ultrasound-guided group and with empty bladder in clinical touch group. In both clinical touch and ultrasound group, the clinicians started the ET in the same way, i.e., cleaning the external genitalia with a dry swab before insertion of a sterile speculum into the vagina. The external cervical os was then cleaned with a dry cotton swab and mucus in the cervical canal was removed with a mucus extractor. Embryos were loaded into Wallace sure view and Cook echo tip catheter. The catheter was then handed over to the clinician who inserted it through the cervical canal. At this stage, there was a difference between the two groups.

In the clinical touch group, when the clinician was satisfied with that he had placed the catheter as close to the fundus as possible without touching it, the plunger was depressed; but in the ultrasound group, the ultrasonographer used a transabdominal ultrasound to guide the clinician in the positioning of the tip of the catheter to ~15 mm from the fundus of the uterine cavity. The plunger was then depressed and the air bubbles observed to be expelled from the catheter tip. The embryos were injected over 30 seconds, allowing observation of the movement of the air bubbles into uterine cavity. Removal of the catheter was also monitored by ultrasound and retention of the air bubbles was observed in the fundal position. The catheter was carefully checked under microscope and the embryo retained within the lumen or adherent to the surface of the catheter were reharvasted. The embryo can be clearly identified by air bubbles inserted on either side, which are seen as bright echoes on the ultrasound image.

The clinician was then required to rate the ET procedure in terms of ease of transfer before they left the ET room. The rating system guidelines were:

- **Very easy:** Transfer catheter went straight through the cervix.
- **Easy with some difficulty:** Required the separation of the transfer catheter to advance the sheath of a stiffer catheter to facilitate the transfer.
- **Difficult:** Required in tenculum in addition to those requirement in easy category.

A positive pregnancy outcome was a positive blood pregnancy test performed 2 weeks after the ET and an ultrasound scan showing at least one sac in the uterine cavity 2 weeks after the positive pregnancy test. Statistical analysis: A p value <0.05 was considered to be statistically significant.

RESULTS

The pregnancy rate and implantation rate appeared higher in the ultrasound-guided group but not significant statistically (Tables 1 and 2).

When the analysis was performed controlling for the number of embryos transferred, there was no significant difference in the two groups whether one, two, three

Table 1. Clinical Data of IVF Cycles in Clinical Touch and Transabdominal Ultrasound Groups

Variables	Clinical touch (n = 262)	Ultrasound-guided (n = 320)
Age in years	34.2	33.9
Primary infertility (%)	142/262 = 54.2	165/320 = 51.6
Mean infertility duration in years	6.0	5.6
Cause of infertility		
Unexplained (%)	44/262 = 16.8	63/320 = 19.7
Male %	92/262 = 35.1	112/320 = 35
Only female %	98/262 = 37.4	127/320 = 39.7
Combined %	28/262 = 10.7	18/320 = 5.6
Mean number of embryos available	7.8	6.9
Mean number of embryos transferred	2.56	2.37
Mean number of oocyte retrieved	13.2	12.3
Days after retrieval	3.1	3.2

No significant difference was observed between the two groups.

Table 2. Outcome of ETs Performed with Clinical Touch and Ultrasound Guidance

	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Pregnancy rate (%)	81/262 = 30.92%	119/320 = 37.19%	0.134 NS
Implantation rate (%)	109/672 = 16.22%	149/758 = 19.66%	0.103 NS

NS = Not significant.

Table 3. Outcome of ET in Subgroups

Pregnancy rate in subgroups	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Number of embryo transferred			
One	3/21 = 14.3%	15/55 = 27.27%	0.327 NS
Two	15/72 = 20.8%	24/92 = 26.1%	0.549 NS
Three	63/169 = 37.3%	80/173 = 46.24%	0.116 NS
Age of patients			
≤35-year-old	53/141 = 37.6%	69/186 = 37.1%	0.981 NS
>35-year-old	28/121 = 23.14%	50/134 = 37.31%	0.021 S
Ease of ET			
Very easy	65/174 = 37.4%	85/225 = 37.8%	0.986 NS
Easy with some difficulty	12/62 = 19.35%	25/68 = 36.8%	0.045 S
Difficult	4/26 = 15.38%	9/27 = 33.33%	0.231 NS

NS = Not significant; S = Significant.

Table 4. Pregnancy Rate According to the Position of the Air Bubbles

	Distance of air bubbles from fundus (mm)						No air bubbles	Total
	0-5	6-10	11-15	16-20	21-25	26-30		
Total	13	34	49	14	6	5	4	**125**
Pregnancy	4	13	21	5	2	1	0	**46**
Pregnancy rate (%)	30.77	38.24	42.86	35.71	33.33	20	0	**36.8**

embryos were transferred. When controlled for age of women (≤35 and >35 years old) again the results were not significantly different in ≤35 years of age group but they were statistically significant in age group >35 years old (23.14% vs. 37.31%, respectively). Pregnancy rate in 'easy with some difficulty' ultrasound group was 36.8% vs. 19.35% in comparison to clinical touch group (statistically significant $p < 0.05$). It may be due to precise recognition of position of uterus in ultrasound-guided cases. If we only examined the cases, which were rated 'difficult' the difference in favor of the ultrasound group appeared nonsignificant (Table 3).

Out of 320 ultrasound-guided ET, in 125 patients, distance of air bubbles from fundus was noted. Pregnancy rate according to the position of the air bubbles was calculated. Maximum pregnancy rate was achieved when the distance of air bubble was between 11-15 mm from the fundus. Four cycles were excluded from this analysis because there was no description of the location of air bubbles in these cases (Table 4).

DISCUSSION

Since the IVF pregnancy was achieved, some aspects of the technique have remained largely unchanged,

whilst other have been constantly evolving, the most significant development being in ovulation induction, the use of intracytoplasmic sperm injection (ICSI) and in the development of culture media. Despite these improvements, the majority of the transferred embryos fail to implant. This failure may be due to poor quality embryo, lack of uterine receptivity or the technique of ET itself.[9,10] Defining the factors that are important for successful ET after IVF has been a major issue. Based on the questionnaires distributed amongst highly experienced IVF clinical, Kovacs summarized the answers.[11] The factor that got highest votes was the need to remove hydrosalpinx before treatment. The other important factors in order of priority included absence of bleeding, type of catheter used, not touching the fundus, avoid the use of a tenaculum, removal of all mucus from the cervix, ultrasound details of the cavity before treatment, leaving the catheter in place for at least 1 minute, 30 minutes rest after transfer, dummy transfer before treatment, ultrasonic monitoring of transfer and antiprostaglandins to prevent contractions. Although the clinician rated the importance of ultrasound guidance as 11th of 12 factors, the role of ultrasound monitoring during transfer should receive more emphasis. The cause of low priority of this factor might be due to the inconvenience and inaccuracy of transabdominal ultrasound guidance.

Generally, the positions of air bubble indicate the position of the embryos. It was recommended that the tip of the catheter be positioned 15 mm from the fundus of the uterine cavity to avoid placement of embryos close to the uterine fundus.[7] In our study, the point of placement of embryo was also 15 mm from the fundal limit of the uterine cavity. We could transfer the embryos to the precise place under transabdominal ultrasound guidance. There was no pregnancy in four cases in which air bubbles could not be identified. It is likely that these embryos were misplaced probably due to uterine contractions or technical errors. In two cases embryos remained in the lumen of catheter. In other cases, we suppose that the catheter was inadvertently abutting the internal tubal os and the bubbles disappeared in the tubal canal. Furthermore, we experienced some cases in which the air bubbles moved towards the cornue or the cervix from the position of the tip of the catheter. These observations also suggest that adequate monitoring by ultrasound guidance is very important during ET.

Evidence emerging from 17 to 20 randomized controlled trials comparing ultrasound guidance versus the 'clinical touch' method for ET have been evaluated. Clinical pregnancy rates were found to be statistically significant higher (odd ratio [OR] 1.31-1.50) with transabdominal ultrasound guidance.[7,12] It has been reported that high frequency uterine contractions on the day of embryo transfer hinder IVF-embryo transfer outcome.[13] It was reported that tactile assessment of catheter placement was unreliable.[14]

The outer guiding catheter inadvertently abutted the fundal endometrium or the internal tubal os and intended the endometrium. The transfer catheter was seen to be embedded within the endometrium. Transabdominal ultrasound-guided ET can minimize these endometrial traumas and thus reduce the uterine contractions. As transabdominal ultrasound can supply fine picture of the flexion of the uterus and the curve of the uterine endometrial midline, the clinician can insert the catheter smoothly without endometrial trauma under the monitoring, and stop the catheter before reaching the fundus. If the curve of the uterine endometrial midline is sharp, we stop the outer sheath before intending the endometrium and advance only the inner catheter, which is softer than the outer sheath, upto 15 mm from the uterine fundus. These atraumatic procedures probably contributed to successful ET in the present study because bleeding from the endometrium or the uterine cervix is a significant negative factor for ET, as suggested by Kovacs.[11]

The procedure was readily accepted by the patients who were reassured by the visualization of the transfer process. The acceptance by the clinician was also high with no significant added time, and the procedure was done with more confidence as the catheter is advanced to the fundus of the uterus under ultrasound scan guidance. Furthermore, ultrasound-guided ET may have two additional advantages over clinical touch ET when considering that: i) Blind catheter placement has been shown to result in a malposition of the catheter in >25% of cases, thus indicating that tactile assessment of ET catheter position is unreliable[14] and ii) the depth of the embryo replacement into the uterine cavity influences implantation rates, with high pregnancy rates obtained when the embryos are replaced 15-20 mm from the fundal endometrial surface.[7] Ultrasound assistance in the ET is a pivotal tool for improving pregnancy rate in assisted reproduction irrespective of whether embryos are fresh or frozen and replaced in spontaneous, stimulated or artificially prepared cycles. A report showing that ultrasound-guided ET improves outcome in patients with previous failed IVF cycles provides further evidence in this regard.[12]

CONCLUSION

There was no significant difference in the pregnancy rate when the number of embryos transferred was controlled. Based on the results obtained from the present study, transabdominal ultrasonography guidance appears to be an essential factor for improving the results of ET especially in case of easy with some difficulty ET and in older women.

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■■■■

Cabotegravir and Rilpivirine Injectable Formulation Receives FDA Approval for HIV Treatment

The US FDA has granted approval for cabotegravir and rilpivirine injectable formulation for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed on a stable antiviral drug regimen, with no history of treatment failure. It is indicated for those who have no known or suspected resistance to either cabotegravir or rilpivirine.

This has become the first FDA-approved injectable formulation complete regimen for adults living with HIV. It is given once a month.

The FDA also granted approval for cabotegravir tablet formulation, to be taken in combination with oral rilpivirine for 1 month before initiating treatment with injectable cabotegravir-rilpivirine. This is aimed at ensuring that the medication is tolerated well… (*FDA*)

Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

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"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

Governing Council Members

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Mukul Rohtagi
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Executive Council Members

Deep Malik
Geeta Anand
Dr Uday Kakroo
Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

Indian Journal of Clinical Practice, Vol. 31, No. 9, February 2021

A Case of Biotinidase Deficiency Presenting as Quadriparesis

RAJEEV THAPAR*, KANNAN VENKATNARAYAN†

ABSTRACT

Biotinidase deficiency is a rare disorder with a wide spectrum of neurological, dermatological and immunological dysfunction. Identification of this disorder is important as it is easily treatable and the patients show dramatic response to therapy, besides the fact that it can prove fatal if not diagnosed. We report a case of biotinidase deficiency who presented with quadriparesis, highlighting all these issues.

Keywords: Biotin, biotinidase deficiency

Biotinidase deficiency is a rare metabolic disease with estimated incidence of approximately 1:60,089 newborns. This enzyme is required for the restoration of free biotin from biocytin after it has activated various carboxylases, in the biotin cycle. Absence of biotinidase leads to biotin deficiency, which results in a range of neurological, dermatological and immunological abnormalities.

CASE REPORT

A 46-month-old girl child was referred to our hospital with complaints of episodes of rapid breathing and progressive weakness of all four limbs. Her complaints had started about 3 months prior when she was admitted for a "lower respiratory tract infection", with predominant complaints of rapid breathing. Subsequent to this, she continued to have episodes of rapid breathing, for which she received treatment on OPD basis.

Over a period of time, she developed weakness of all four limbs, predominantly of the proximal muscle group, manifesting as unsteady gait and inability to self-feed. The weakness progressed and she was bedridden at the time of admission (Fig. 1). There was also history of one episode of generalized clonic-tonic seizures 2 weeks prior. She was a product of a nonconsanguineous marriage, with no remarkable delay in attaining the target developmental milestones. Her elder brother had died following similar clinical manifestations of progressive weakness at 4 years of age. In fact, this heightened the parental anxiety to seek medical help. Clinically, she was alert and had silent tachypnea. Skin manifestations in form of candidal lesions of the axilla (Fig. 2) and the toe clefts (Fig. 3) along with alopecia were present (Fig. 4). The bilateral plantars were extensor with gross hypotonia and the power in the proximal muscles of both limbs being Grade II (as per Medical Research Council Grading System of United Kingdom). Baseline investigations revealed partially compensated metabolic acidosis. Magnetic resonance imaging (MRI) studies showed mild cerebral atrophy with hypoplasia of cerebellar vermis. MRI of spine was suggestive of myelopathy (Fig. 5). Cerebrospinal fluid (CSF) study, ophthalmologic and audiological evaluations were normal.

In view of family history and the episodic nature of respiratory complaints suggestive of metabolic acidosis, along with the skin manifestations, possibility of neurometabolic syndrome was considered. Serum lactate was elevated (31 mg/dL [4.5-19.8 mg/dL]) and the biotinidase activity was 0 nmol/min/mL. The child was started on daily oral biotin 20 mg and made significant recovery. Hyperventilation subsided in 12 hours; the child could sit without support in 2 days and started walking in the second week of treatment. Skin lesions healed in the third week and there was hair growth.

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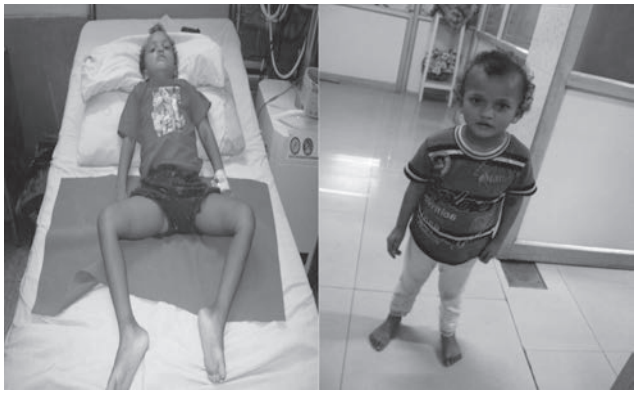

Figure 1. Patient presenting with hypotonia and quadriparesis (left panel) and improvement following biotin replacement therapy (right panel).

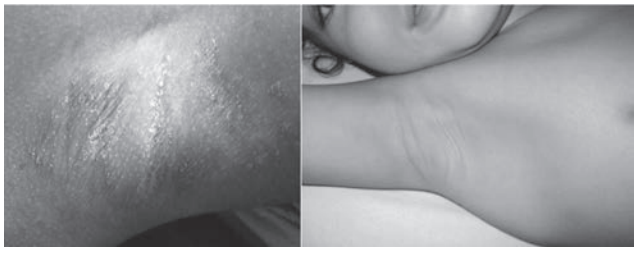

Figure 2. Axillary candidal skin lesions before (left panel) and after treatment (right panel).

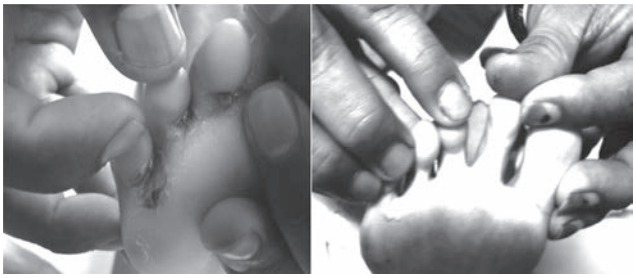

Figure 3. Candidiasis of toe clefts before (left panel) and after treatment (right panel).

Figure 4. Note the degree of alopecia in a 4-year-old girl child.

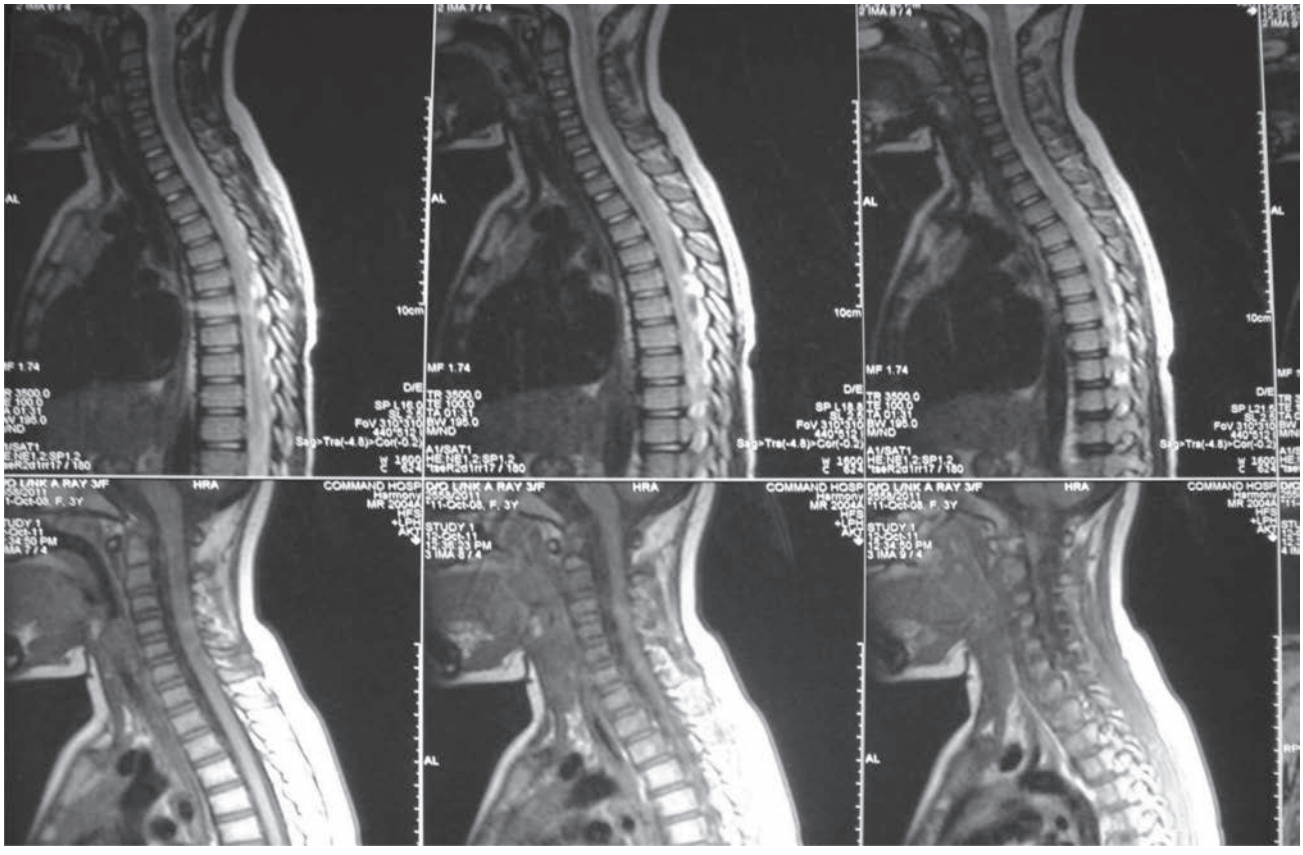

Figure 5. MRI cervical spine showing hyperintensities suggestive of myelopathy.

DISCUSSION

Biotinidase is an essential enzyme required for recycling biotin by lysing lysine moiety from biocytin, as elucidated in the biotin cycle. Deficiency of biotinidase results in the deficiency of biotin, which is required as a catalyst for the carboxylase systems in the body. The four main carboxylase systems being: 1) Pyruvate carboxylase (required for glucose production; inactivity lowers blood sugar resulting in hypoglycemia and lactic acidosis); 2) acetyl-CoA carboxylase (required for biosynthesis of fatty acids by liver and fat cells; inactivity results in reduced availability of stored fatty acids for exercise resulting in hypotonia); 3) propionyl-CoA carboxylase (required for breakdown of amino acids with an odd number of carbons; inactivity results in propionic academia and reduced activity of citric acid cycle resulting in reduced energy production in the brain, resulting in developmental delays) and 4) methylcrotonyl-CoA carboxylase (required for breakdown of leucine; inactivity results in lowered carnitine levels and methylcrotonylglycinuria).

Although, individual deficiencies of all four carboxylases have been reported, the clinical spectrum varies widely from a severe form presenting early (multiple carboxylase deficiency, holocarboxylase synthase deficiency) to milder varieties presenting late (biotinidase deficiency).

The clinical presentation of repeated episodes of hyperventilation, progressive neurological deterioration with skin lesions, corroborating with laboratory features of lactic acidosis suggested the diagnosis of biotinidase deficiency in this case.

The clinical spectrum of biotinidase deficiency depends on the severity of the defect. The clinical manifestations predominantly include neurological, skin and respiratory manifestations. The neurological spectrum includes seizures, hypotonia and developmental delay in the early period. Some older children present with progressive spastic quadriparesis, hearing and visual impairment. The present case had muscle weakness. In view of the clinical presentation and previous case reports of recurrent myelopathy, MRI of spine was done, which was suggestive of myelopathy (Fig. 5). Seborrheic dermatitis, alopecia and candidal infections due to immunological dysfunction are the predominant skin manifestations and our patient had most of these features. Metabolic acidosis resulting in hyperventilation often masquerades as a primary respiratory illness, as in this patient.

Identification of this disorder is important as it can be treated with supplementation of biotin. Lifelong supplementation up to 40 mg/day is needed that results in both clinical and radiological improvement.

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Case Report of Atypical Scar Endometriosis

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ABSTRACT

Scar endometriosis is a rare type of extrapelvic endometriosis that is associated with obstetrical and gynecological surgeries. Scar endometriosis is reported in only 0.03-0.15% of all cases of endometriosis. We are reporting a case of 39-year-old female patient presenting with scar endometriosis 10 years after her last lower segment cesarean section (LSCS). The patient came to the Gynecology OPD, NIUM Hospital on 6th May 2019 with the complaint of suprapubic swelling since 6 months, which was growing slowly. Her menstrual history was regular, but she had lower abdominal pain during menstruation. Patient had 2 children delivered by LSCS. On clinical history, examination, USG and FNAC finding, the swelling was diagnosed as scar endometriosis.

Keywords: Endometriosis, abdominal scar, LSCS and prevention

Endometriosis refers to the presence of endometrial glands and stroma outside the uterus. It is estimated to affect 10-15% of all women of reproductive age, i.e., 18-45 years, and 70% of women who have chronic pelvic pain. Endometriosis occurs in abdominal, extra-abdominal and remote areas. Scar endometriosis is reported in only 0.03-0.15% of all cases of endometriosis. Several factors have been consistently associated with risk for endometriosis, such as early age at menarche, late menopause, frequent menstrual cycles, low parity, use of estrogen pills, estrogen producing tumors, obesity. The cause of endometriosis is unclear, but several theories have been reported. One possible mechanism is retrograde menstruation. This retrograde flow, along with potential hematogenous or lymphatic circulation, may result in the seeding of endometrial tissue in ectopic sites. Another theory is direct implantation of endometrial tissue during surgical procedures like lower segment cesarean section (LSCS), hysterectomy, myomectomy, episiotomy, etc. Other factors, such as genetic, environmental, hormonal, inflammatory or immunological, may also result in implantation of endometrial tissues on ectopic sites.

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Clinical presentation of endometriosis varies in different women. Patients often present with symptoms such as intermenstrual bleeding, dysmenorrhea, dyspareunia, dyschezia and dysuria. Pelvic pain may present before onset of menstruation. Often, endometriosis can be asymptomatic, only diagnosed during evaluation for infertility. The lesions can be peritoneal lesions, superficial implants or cysts on the ovary, or deep infiltrating disease. Classification of endometriosis associated symptoms has been established by the American Society for Reproductive Medicine (ASRM) based on the morphology of peritoneal and pelvic implants such as red or pink, white and black lesions, percentage of involvement of organ. Endometriosis in bowel, urinary tract, fallopian tube, vagina, cervix, skin or other locations are identified as per ASRM guidelines. Stages of endometriosis according to ASRM guidelines are stage I, II, III and IV. These are based on the point scores and correspond to minimal, mild, moderate and severe endometriosis. Early diagnosis and intervention could ultimately improve the quality of life and preserve fertility.

OBJECTIVE

The goal of this paper is to highlight an atypical case of scar endometriosis.

CASE REPORT

A 39-year-old female patient came to Gynecology OPD of National Institute of Unani Medicine (NIUM), Hospital on 6th May 2019 with the complaint of suprapubic swelling, which was gradually increasing in size since last 6 months. She also complained that

the pain in lump is worse during menstruation. Her age of menarche was 15 years. She was having regular menstruation with normal flow, but history of dysmenorrhea was present. She had no history of any other systemic illness. Her married life was 18 years. She had 2 children, both were delivered by LSCS, and history of 1 spontaneous abortion was also present. The patient was tubectomized after cesarean section. Her last child birth was 10 years back. According to her history before surgery, she was fit and well with no documented history of endometriosis. Vitals were normal and her body mass index (BMI) was 26.2 kg/m^2.

On examination, a suprapubic swelling of approximately 8 × 5 cm was found at the site of lower part of cesarean scar. On palpation, local temperature was raised, mass was irregular extending to pelvic region (Fig. 1). On vaginal examination, uterus was found anteverted, bulky, mobile and fornices free. On initial examination, it was diagnosed as a lump. Consultant gynecologist advised for ultrasonography (USG) and cytology of lump. USG was done on 14/5/2019; findings showed large well-defined hypoechoic solid lesion approximately 8.6 × 6.5 × 7.1 cm noted in subcutaneous plane in midline of lower anterior abdominal wall and suprapubic region, suggestive of endometriosis. For confirmation, fine needle aspiration cytology (FNAC) was done on the same day, i.e., 14/5/2019, which reported benign cellular stromal fragments of endometrium with occasional benign glands. No granuloma or malignancy was found. These findings suggested endometriosis. Extra-abdominal endometriosis occurs at the time of surgical procedures like myomectomy, hysterectomy or LSCS, etc. Here in this case, previous history of 2 LSCS was present, which suggested the swelling may be due to direct implantation of endometrial tissue during cesarean section. This endometrial tissue grows every month in response to hormones especially estrogen. Estrogen helps in proliferation of endometrial tissue every month, hence, the suprapubic swelling was increasing slowly.

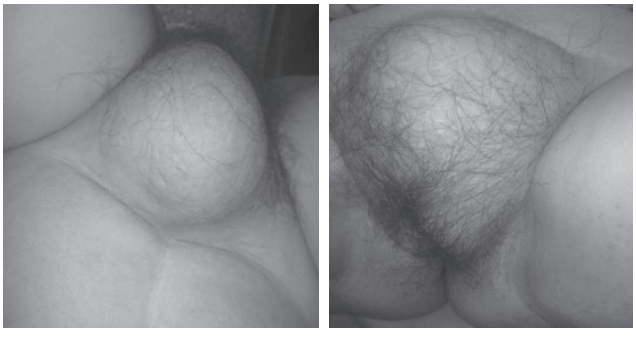

Figure 1. Pubic swelling.

DISCUSSION

Scar endometriosis is a rare entity that usually follows previous abdominal surgery, especially early hysterectomy and cesarean section. There are numerous sites where extrapelvic endometriosis has been reported. These include lungs, pleura, bladder, kidney, bowel, omentum, umbilicus and abdominal wall. Endometriosis involving the abdominal wall is a rare occurrence; however, it should be considered in the differential diagnosis of abdominal wall masses in females. The typical clinical scenario involves a parous female with a history of gynecological or obstetric surgery presenting with a painful nodule or lump. The severity of pain and size of the lump may vary with menstrual cycle. In this case, the patient remained without a diagnosis for 10 years. Gynecological history and physical examination is important in finalizing the diagnosis. The history revealed that the pain coincided with her menstrual cycle. The clinical examination revealed a soft, nonreducible swelling located in pubic region. It was tender on palpation. On initial examination, it was diagnosed as a lump. Based on the gynecological history of a cyclical increase in the size and severity of pain, an endometrioma was also included in the differential diagnosis.

Surgical scar endometriosis is believed to result from deposits of endometrial cells during surgical intervention. These cells are then stimulated by estrogen to produce endometriomas. Although relatively uncommon, it was well-documented in clinical practice that scar endometriosis occurs with different types of incisions where contact has possibly occurred with endometrial tissue. The endometriomas may develop 1-20 years postoperatively; examples include cesarean section, laparoscopy, tubal ligation and hysterectomy. Of these, cesarean section and hysterectomy are the most common. The incidence after cesarean section is difficult to determine, but estimates range from 0.03% to 0.47%. Minaghlia et al analyzed 30 years of incisional endometriosis after cesarean section and reported the incidence of scar endometriosis to be 0.08%. Frequency of scar endometriosis increases by number of cesarean section and laparoscopy performed in recent years. Other authors have reported an incidence of 0.2% in all cesarean sections performed. To make a definitive preoperative diagnosis of endometriosis is difficult.

Positive histology confirms the diagnosis of endometriosis; however, negative histology does not rule it out. Additionally, it is controversial if histology should be obtained if there is only peritoneal disease. Visual inspection usually suffices, but histological confirmation of at least one lesion is ideal. In comparison with

laparoscopy, transvaginal ultrasound seems to have no value in diagnosis of peritoneal endometriosis. However, it is a potential tool to make and exclude the diagnosis of ovarian endometrioma. Transvaginal sonography (TVS) may have a role in the diagnosis of disease involving the bladder or rectum. Medical imaging plays a role in locating the mass and ruling out hernia and other conditions, for example lipoma, abscess and suture granuloma. Magnetic resonance imaging (MRI) remains the most useful imaging modality to exclude other pathology. In this case, the scar endometriosis was diagnosed by USG and was confirmed by FNAC of the lump.

CONCLUSION

Endometriosis is a debilitating disease that impacts the quality of life of adolescent and adult patients. Delayed diagnosis is common and may lead to a decline in reproductive potential and fertility. A semi- or non-invasive diagnostic biomarker would be a useful tool to identify patients early in the disease process, thus improving outcomes, including less pain and better fertility. The occurrence of abdominal wall scar endometriosis after cesarean section has been a definite entity; steps to prevent this complication have not been explained. Literature recommends that cleaning, irrigation with saline and closure of abdominal wound will prevent scar endometriosis.

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Ethylene Dibromide Poisoning with Acute Myocarditis: A Rare Association

MAHESH DAVE*, ANIRUDDHA BURLI†, RAMIT SINGH PALA†, SAHIL KHARBANDA‡, MANASVIN SAREEN‡

ABSTRACT

Ethylene dibromide (EDB) is a commercially available fumigant used as a pesticide. Its toxicity may develop from poisoning after ingestion. It principally affects liver and kidneys causing centrilobular necrosis and tubular injury, respectively. We report a case of suicidal ingestion of EDB in a 29-year-old male. The patient presented with predominant gastrointestinal symptoms and hypotension. Upon further investigation, the patient had electrocardiograph changes and evidence of myocarditis. Prompt symptomatic treatment resulted in favorable outcome and patient was discharged. Hence, myocarditis, though rare, is yet a significant presentation of EDB poisoning.

Keywords: Poisoning, ethylene dibromide, myocarditis

Ethylene dibromide (EDB) or dibromoethane, also known as bromo fume, is a volatile, non-inflammable, colorless liquid with a sweet chloroform like odor. It is used as a solvent for resins, gums and waxes. The other uses of this chemical are as lead scavengers in gasoline as well as pesticide for grains, fruits and vegetables.

EDB is very toxic for human beings and is absorbed through skin, inhalation and ingestion and can cause acute toxicity. It is commercially available in the form of 3 mL or 5 mL ampoule easily in India and many other countries. The toxic dose varies from 5 to 10 mL (1-2 ampoules) causing severe liver and renal damage.

Acute toxic effects commonly observed after ingestion of EDB may be pain abdomen, nausea, vomiting, giddiness, headache, drowsiness and severe toxic effects may be in the form of liver and kidney involvement, subsequently causing hepatorenal failure and death.

Acute myocarditis is a very rare presentation reported following acute EDB poisoning and not documented in literature worldwide. Hence, we report this case of EDB poisoning presenting with acute myocarditis without hepatic or renal involvement, which is the rarest association.

CASE REPORT

A 29-year-old male was admitted in emergency medical ward with history of EDB pesticide ingestion 4 hours prior to admission. He consumed 2 ampoules (3 mL each) mixed with approximately 100 mL of water with suicidal intent. He had history of nausea, vomiting, pain abdomen, headache and giddiness at the time of admission. Past history revealed no existing comorbidities including any form of psychiatric illness.

His general physical examination was unremarkable. Vitals examination at the time of admission revealed pulse of 112 bpm, regular, normal volume. Blood pressure was 90/60 mmHg. Rest vital signs were within normal limit. Systemic examination revealed no significant abnormality.

In view of EDB poisoning and our past experiences, the patient was investigated for complete blood count (Hemoglobin - 11.3 g%, total leukocyte count [TLC] - 6,470 cells/mm^3, platelets - 1.25 lakh/mm^3), renal function test (blood urea - 29.9 mg/dL, serum creatinine - 0.93 mg/dL), liver function test (serum bilirubin - 0.4 mg/dL, serum glutamic oxaloacetic transaminase [SGOT] - 14 IU, serum glutamic pyruvic transaminase [SGPT] - 23 IU, alkaline phosphatase [ALP] - 72 IU),

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serum electrolytes and urine examination at the time of admission and the values were found within normal limits.

His arterial blood gas (ABG) analysis done at the time of admission showed pH - 7.31, partial pressure of oxygen (PaO_2) - 92 mmHg, partial pressure of carbon dioxide ($PaCO_2$) - 38 mmHg, serum bicarbonate (HCO_3) - 19 mmol/L and arterial oxygen saturation (SaO_2) - 96.4%, suggestive of metabolic acidosis. Subsequent ABGs were found normal.

Patient was put on routine management protocol of poisoning which included gastric lavage, use of activated charcoal and milk of magnesia along with fluid management. But even after fluid challenge, his blood pressure was persistently low and hence, he was investigated with electrocardiogram (ECG) and X-ray chest.

X-ray chest showed no cardiopulmonary abnormality.

His first ECG done 2 hours post-hospitalization showed heart rate 102/min with prolonged PR interval (0.22 s) with ST-segment elevation (concave upwards) with associated T inversions in leads V1 to V4 which was suggestive of acute myocarditis (Fig. 1).

In view of acute myocarditis, further confirmation was done with help of cardiac biomarkers, which included creatinine phosphokinase-MB (CPK-MB) and serum troponin T levels, which were found significantly elevated. CPK-MB was 74 U/L (Normal 0-25) and Trop T was 0.12 (Normal 0-0.01).

Patient was followed up regularly for 5 days with serial ECG and cardiac biomarkers.

Day 2 ECG showed heart rate 96/min with persistent ST-segment elevation in V1 to V4 with T inversions in V1 to V6 and normal PR interval (Fig. 2).

Day 3 ECG showed heart rate 52/min with ST-segment depression in II, III and aVF; ST-segment elevation in V1 and V2 with symmetrical T inversions in V1 to V6 (Fig. 3).

Day 4 ECG showed heart rate 42/min with ST-segment elevation in V1 and V2 (less than previous ECG) with normal T waves and PR interval (Fig. 4).

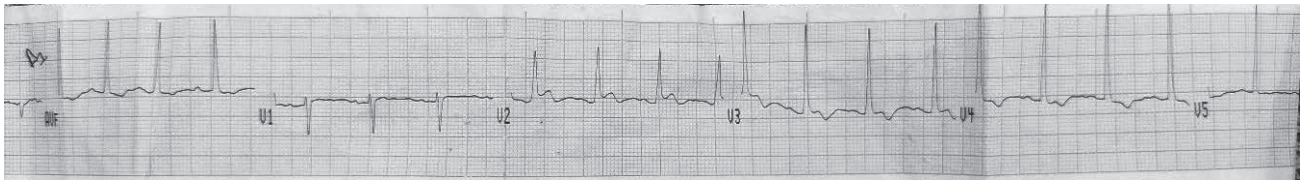

Figure 1. Day 1 - heart rate 102/min. PR interval (0.22 s). ST-segment elevation (concave upwards) with T inversions in leads V1 to V4.

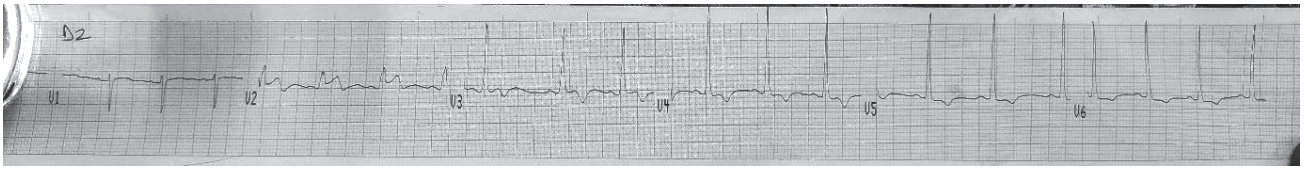

Figure 2. Day 2 - heart rate 96/min. ST-segment elevation in V1 to V4. T inversions in V1 to V6.

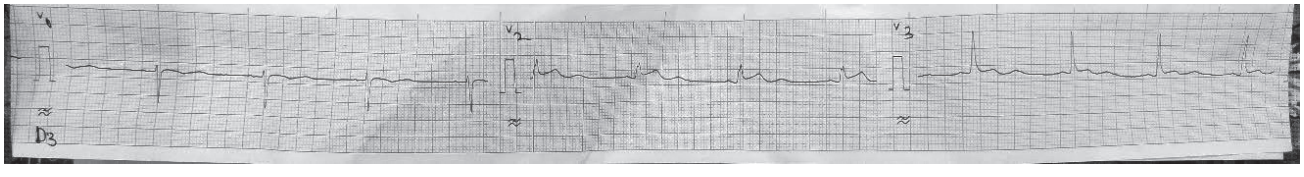

Figure 3. Day 3 - heart rate 52/min. ST-segment depression in II, III and aVF. ST-segment elevation in V1 and V2 with symmetrical T inversions in V1 to V6.

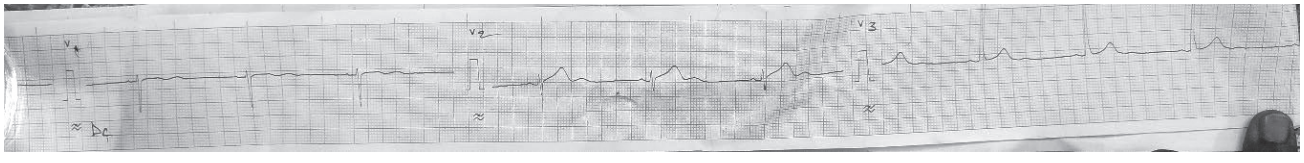

Figure 4. Day 4 - heart rate 42/min. ST-segment elevation in V1 and V2.

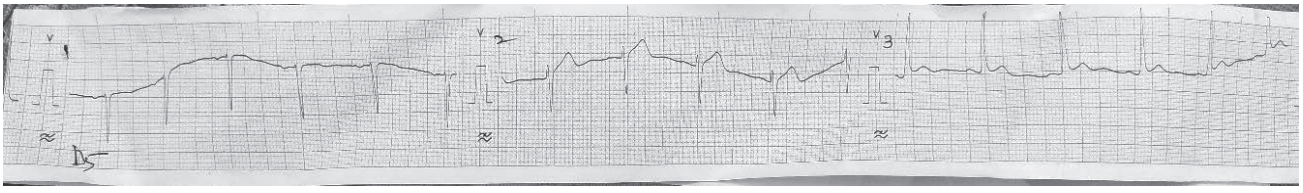

Figure 5. Day 5 - heart rate 84/min. ST-segment elevation in V1 and V2.

Day 5 ECG showed heart rate 84/min with ST-segment elevation in V1 and V2 (less than previous ECG) with normal T waves and PR interval (Fig. 5).

Serial CPK-MB and Trop T returned to normal after remaining persistently high for 4 days.

Further, 2-dimensional cardiac echocardiography revealed no significant abnormality with left ventricular ejection fraction (LVEF) of 60-65%, except for minimal pulmonary regurgitation.

Patient was managed by giving IV magnesium sulfate, IV hydrocortisone, carnitine, IV fluids, vitamin C and E. His blood pressure started improving 12 hours after treatment and was discharged after 5 days with advice for relative bed rest, vitamin C and E and carnitine therapy and follow-up at medical OPD.

DISCUSSION

Ethylene dibromide is a halogenated hydrocarbon which is colorless and available in Indian market as pure form in 3 mL and 5 mL ampoules, commonly used as grain preservative. It is well-absorbed from skin, respiratory and gastrointestinal tracts, metabolized in liver and excreted through kidney via urine as bromide conjugates of glutathione and L-acetyl cysteine. EDB is metabolized by two pathways.

A conjugated pathway catalyzed by glutathione S-transferase and oxidative pathway catalyzed by cytochrome P-450. The exact mechanism of acute EDB toxicity is yet not well-understood. Lipid peroxidation and liberation of free radicals damage membrane structure, resulting in acute liver injury (fulminating hepatitis, hepatic necrosis) and acute tubular necrosis of kidneys, leading to acute hepatorenal failure and death.

EDB poisoning is very uncommonly reported in literature. A very few autopsy reports in EDB poisoning available in literature suggest centrilobular necrosis, Kupffer cell damage, acute tubular necrosis, pulmonary edema and muscle necrosis as major findings.

Cardiac involvement in acute EDB poisoning is yet not reported in any case worldwide. In our patient, cardiac involvement was observed 3-4 hours after poisoning. The etiology of cardiac involvement is not known but probably is due to free radical-induced membrane peroxidation.

In this view, patient was treated with membrane stabilizing agent (magnesium sulfate), free radical scavengers (vitamin C and E, carnitine) and we were able to normalize the ECG changes and cardiac biomarkers on the 5th day.

CONCLUSION

In Southern Rajasthan, EDB is a common pesticide used for grain preservation and a common poisoning agent after organophosphate and celphos. The incidence of death in these cases is very high and maximum deaths are due to late hepatorenal failure. Cardiac involvement is rarely seen in EDB poisoning but careful evaluation is essential as it occurred in our case. Early detection of cardiac involvement and prompt treatment may save the life of the patients.

SUGGESTED READING

1. Prakash MS, Sud K, Kohli HS, Jha V, Gupta KL, Sakhuja V. Ethylene dibromide poisoning with acute renal failure: first reported case with non-fatal outcome. Ren Fail. 1999;21(2):219-22.
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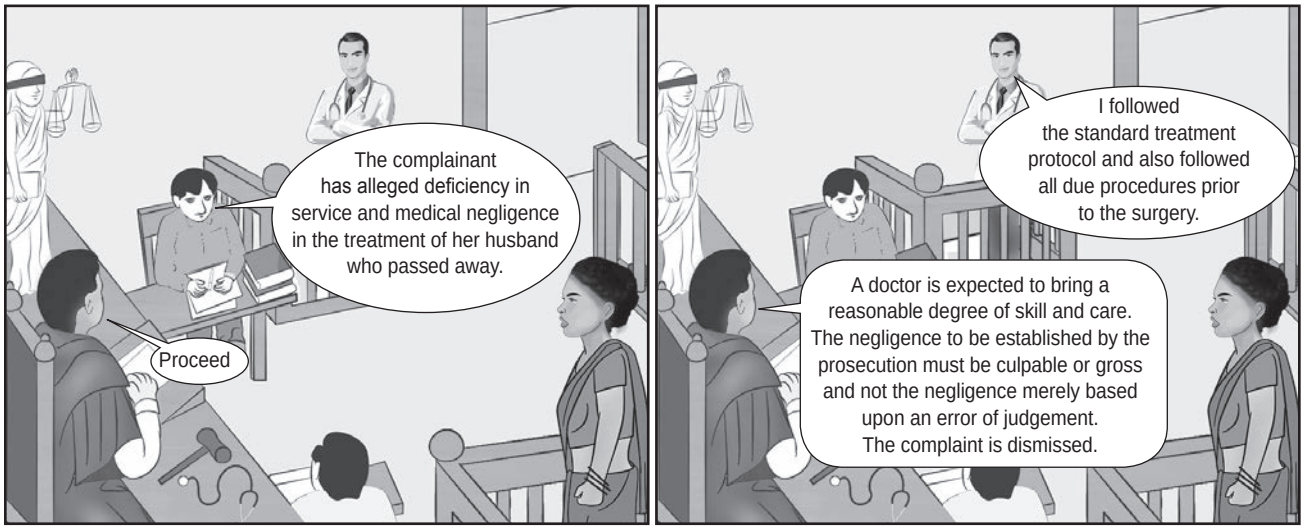
4. Singh N, Jatav OP, Gupta RK, Tailor MK, Jain R. Outcome of sixty four cases of ethylene dibromide ingestion treated in tertiary care hospital. J Assoc Physicians India. 2007;55:842-5.

Indian Journal of Clinical Practice, Vol. 31, No. 9, February 2021

A Medical Practitioner is not Expected to Achieve Success in Every Case That He Treats



Lesson: In its judgement in *Kusum Sharma & Ors vs Batra Hospital & Medical Research Centre & Others on 10 February, 2010 Civil Appeal No.1385 of 2001*, the Supreme Court of India said "Merely because a complication occurs, it does not mean that the hospital or the doctor was guilty of negligence. A medical practitioner is not expected to achieve success in every case that he treats. The duty of the doctor is to exercise reasonable skill and care. A medical practitioner would be liable only where his conduct fell below that of the standards of a reasonably competent practitioner in his field."

COURSE OF EVENTS

- 10.12.1989: Patient visited Hospital 'X' with complaints of swelling and difficulty in breathing while climbing stairs. He was very obese and also had high blood pressure. No diagnosis could be made.
- 14.3.1990: Patient was examined by Dr 'A' (*Respondent No. 2*) and Dr 'B' at Hospital 'Y' (*Respondent No. 1*) and was advised admission.
- 20.3.1990: After admission, ultrasonography (USG) abdomen was done followed by computed tomography (CT) scan of abdomen on the next day, which revealed a large left adrenal mass, for which he was advised surgery.
- 2.4.1990: Surgery done by Dr 'C' (*Respondent No. 3*) to remove the abdominal tumor after taking consent from the appellants. Tumor was found to be malignant on testing. Pancreas was damaged during surgery, and a drain was fixed to drain out fluids.
- 23.5.1990: A second surgery was done to control the flow of fluids in Hospital 'Y' by Dr 'D' (*Respondent No. 4*) assisted by Dr 'C' (*Respondent No. 3*) after taking consent from the wife of the patient.
- 23.6.1990: Patient was discharged with two bags on his body and an advice to follow-up and change of the dressing regularly.
- 14.7.1990: Respondent Nos. 2 and 3 visited the residence of the deceased and found him in a bad condition and asked him to go to AIIMS where he was admitted on 22.7.1990 and treated for pancreatic fistula and chronic fistula. He was discharged on 26.7.1990 with an advice to follow-up in the OPD.
- 30.9.1990: Patient was admitted in a hospital outside Delhi where he was diagnosed as having postoperative complications of adrenalectomy and gluteal abscess. He was discharged on 3.10.1990 with an advice to get further treatment at AIIMS.
- 9.10.1990: The patient vomited at home and was shifted to Hospital 'Y'.

- 11.10.1990: The patient died due to pyogenic meningitis.

The patient's wife (*Appellant No. 1*) filed a complaint in the Supreme Court under Section 21 of Consumer Protection Act, 1986 alleging deficiency in services and medical negligence on the part of the doctors (including the hospital) in the treatment of her husband and claimed a compensation of ₹ 45 lakhs.

ALLEGATIONS

- No informed consent.
- Preoperatively only USG and CT done to establish the nature of the tumor.
- The deceased had no access to any of the hospitals records before filing the complaint.
- There was nothing on record to conclusively establish malignancy of the tumor prior to the surgery. Appellants had not been informed about the possible surgical complications and alleged that the pancreatic abscess was due to the pancreas being injured during surgery.
- Doctors lacked the experience and skill required to undertake such a complicated operation.
- The appellants also had the grievance that they were not informed in time of the damage caused to the body of pancreas and removal of the spleen. When this fact came to the notice of the deceased, he asked for the details which were not given.
- The 'anterior' approach to remove the left adrenal mass during the first surgery was incorrect and not the standard approach. The 'posterior' approach should have been used instead.
- The appellants alleged that the tumor taken out from the body was not malignant.

SOME SALIENT COURT OBSERVATIONS

- Respondent No. 3: "*… anterior approach was preferred over the posterior approach in the suspected case of cancer. The risk involved was explained to the patient and the appellants and they had agreed to the surgery after due consultation with the family doctor.*" Literature from medical texts was cited for adopting 'anterior' approach supported by two expert witnesses as well…
- Respondent No. 4: "*…there are three well known alternative methods of food supply of nutrition minimizing any leakage of enzymes from the pancreas. Any of the alternative methods could be adopted only after opening the stomach ...*"
- "*…there was not even a whisper of any incision or draining of gluteal abscess. The Essentiality Certificate makes it clear that no incision was made to drain out gluteal abscess.*"
- Dr 'E' *(on behalf of Respondent No. 1):* "*… although the respondents fully sympathized with the appellants' unfortunate loss, the respondents are constrained to submit that the appellants had presented a malicious, fabricated and distorted account to create a false impression that the respondents were guilty of negligence…*"
- "*30…appellants have ignored the fact that the medicine is not an exact science involving precision and every surgical operation involves uncalculated risks and merely because a complication had ensued, it does not mean that the hospital or the doctor was guilty of negligence. A medical practitioner is not expected to achieve success in every case that he treats. The duty of the Doctor like that of other professional men is to exercise reasonable skill and care. The test is the standard of the ordinary skilled man… death was attributable to the serious disease with which he was suffering from…*"
- "*32. … It was clearly recorded in the operation transcript that the body of the pancreas was damaged on its posterior surface. The said fact was recorded in the discharge summary.*"
- The operating surgeons "*were not obliged to follow every detail of expert recommendation as appropriate decisions were to be made in accordance with the findings at surgery.*" The respondents denied any injury to the stomach or that any procedure adopted by them in surgery endangered the life of the patient.
- After following the 2nd surgery, the patient "*did not maintain any contact with the answering respondents till 9.10.1990 barring one visit to Respondent No. 2 on 31.8.1990 for the purpose of obtaining fitness certificate. The answering respondent cannot be held responsible for any mishap, which might have taken place when the deceased… was being treated elsewhere.*" Also, "*no request was received by Respondent No. 1 from AIIMS for supply of the case sheets or the tumor mass.*"
- The patient was brought to Hospital 'Y' in a critical condition when the disease (pyogenic meningitis) had become very advanced.
- The diagnosis of cancer was not an '*afterthought*' as alleged, but was a "*considered one*" after two histopathological reports. All reference to cancer had been deleted from the discharge summary prepared initially on request of the appellants as it would have mentally disturbed the patient.

- Dr 'C' has impressive credentials and had undertaken training in a well-known cancer hospital in the country and was sufficiently experienced to handle a surgery of this nature.

The Court examined the laws on negligence and also explained the nature of evidence required to establish civil and criminal negligence.

- *"… the law of negligence has to be applied according to the facts of the case."*
- *"49. In Bolam v. Friern Hospital Management Committee (1957) I WLR 582: (1957) 2 All ER 118 (Queen's Bench Division - Lord Justice McNair observed … The direction that, where there are two different schools of medical practice, both having recognition among practitioners, it is not negligent for a practitioner to follow one in preference to the other accords also with American law… a failure to warn the patient of dangers of treatment is not, of itself, negligence."*
- *"… Every surgical operation is attended by risks. We cannot take the benefits without taking risks. Every advancement in technique is also attended by risks."*
- *"59… A doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men in that particular art."*
- *"60. The test is the standard of ordinary skilled man exercising and professing to have that special skill."*
- *"66 ... a clear distinction exists between "simple lack of care" incurring civil liability and "very high degree of negligence" which is required in criminal cases…"*
- *"67... There is a marked difference as to the effect of evidence, viz. the proof, in civil and criminal proceedings. In civil proceedings, a mere preponderance of probability is sufficient, and the defendant is not necessarily entitled to the benefit of every reasonable doubt; but in criminal proceedings, the persuasion of guilt must amount to such a moral certainty as convinces the mind of the Court, as a reasonable man, beyond all reasonable doubt. Where negligence is an essential ingredient of the offence, the negligence to be established by the prosecution must be culpable or gross and not the negligence merely based upon an error of judgement."*
- *"69. In a landmark judgement in Jacob Mathew v. State of Punjab & Another (2005) 6 SCC 1, the Court observed as under: A lawyer does not tell his client that the client shall win the case in all circumstances. A physician would not assure the patient of full recovery in every case. A surgeon cannot and does not guarantee that the result of surgery would invariably be beneficial, much less to the extent of 100% for the person operated on. The only assurance which such a professional can give or can be understood to have given by implication is that he is possessed of the requisite skill in that branch of profession which he is practising and while undertaking the performance of the task entrusted to him he would be exercising his skill with reasonable competence...*
- *"78. A doctor faced with an emergency ordinarily tries his best to redeem the patient out of his suffering. He does not gain anything by acting with negligence or by omitting to do an act… it will be for the complainant to clearly make out a case of negligence before a medical practitioner is charged with or proceeded against criminally."*
- *"80. The professional should be held liable for his act or omission, if negligent… at the same time courts have to be extremely careful to ensure that unnecessarily professionals are not harassed and they will not be able to carry out their professional duties without fear."*
- *"90 (2) … A simple lack of care, an error of judgement or an accident, is not proof of negligence on the part of a medical professional. So long as a doctor follows a practice acceptable to the medical profession of that day, he cannot be held liable for negligence merely because a better alternative course or method of treatment was also available or simply because a more skilled doctor would not have chosen to follow or resort to that practice or procedure which the accused followed."*
- *"90 (3) The standard to be applied for judging… would be that of an ordinary competent person exercising ordinary skill in that profession. …A highly skilled professional may be possessed of better qualities, but that cannot be made the basis or the yardstick for judging the performance of the professional proceeded against on indictment of negligence."*

FINAL JUDGEMENT

"95. … As long as the doctors have performed their duties and exercised an ordinary degree of professional skill and competence, they cannot be held guilty of medical negligence. It is imperative that the doctors must be able to perform their professional duties with free mind."

The Court observed that the "*Appellants have failed to make out any case of medical negligence against the respondents.*" The Hon'ble Court concurred with the National Commission in dismissing the complaint of the appellants as being devoid of any merit. The Court also directed all the parties to bear their own costs.

REFERENCE

1. Kusum Sharma & Ors vs Batra Hospital & Medical Research Centre & Others on 10 February, 2010 Civil Appeal No. 1385 of 2001.

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Medtalks with Dr KK Aggarwal

Infectious Diseases Society of America (IDSA) Panel Updates Guidelines on COVID Molecular Diagnostic Tests

- The panel noted that saliva tests were particularly effective if the test included instructions to cough or clear the throat prior to spitting into the tube.
- Using a throat swab alone was less effective and missed more cases compared to other methods.
- Recommendation: A saliva test or swabs from either the middle or front of the nose are preferable over a throat swab alone.
- A combination of saliva and swabs from the front and middle of the nose and throat together appeared equivalent to the gold-standard deep swab.
- Saliva samples do have challenges. A laboratory must validate that its systems are able to handle the stickier material. Additionally, asking a patient to cough necessitates more personal protective equipment (PPE) for the healthcare professional.
- The only rapid isothermal test that had enough data on which to issue a recommendation was the ID NOW test (Abbott Labs). (*Medscape*)

Early Use of High-titer Plasma

Administering convalescent plasma with high levels of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within the first 3 days of symptoms was tied to significantly lower odds of progression to severe COVID-19. A trial of 160 older adults with COVID-19 randomized half to receive plasma and half to receive placebo infusion. Treatment with high-titer plasma decreased the relative risk for severe disease by 48% in an intent-to-treat analysis.

"Not any plasma, not any time," stated senior author Fernando Polack. The key is to select plasma in the upper 28th percentile of IgG antibody concentrations and to administer therapy before disease progression. The study was published online in *The New England Journal of Medicine*. (*Medscape*)

HCFI Round Table Expert Zoom Meeting on "Consensus Document on COVID-19 Vaccine Myths"

9th January, 2021 (11 am-12 pm)

Participants: Dr KK Aggarwal, Dr Jayakrishnan Alapet, Dr Suneela Garg, Prof Mahesh Verma, Dr Anita Chakravarti, Dr Ashok Gupta, Dr DR Rai, Dr Balbir Verma, Mr Bejon Misra, Ms Upasana Arora, Dr KK Kalra, Dr Anil Kumar, Ms Ira Gupta, Dr S Sharma

Consensus Statement of HCFI Expert Round Table

- Several myths and concerns about the vaccine are circulating in society.
- A major concern is will the vaccine work on the mutant strain? Will it produce a new strain?
- Killed vaccines are safe; since they produce fewer antibodies, they require multiple doses (as also with rabies vaccine). E.g., Rabies vaccine (there are two types of rabies vaccine and both of them are killed vaccines), DPT vaccine (pertussis component is a killed vaccine).
- Phase 3 trial examines safety; the only vaccine which can be launched early is a killed vaccine.
- Vector vaccine and mRNA vaccines are being used for the first time. The only vector vaccine is dengue vaccine, which is not universally accepted.
- Each time a virus mutates, it takes away the unwanted amino acids. Deletion of amino acids causes the virus to increase its infectivity.
- The D614G is the strain which is prevalent all over the world. This mutation is in the S1 protein but after receptor-binding domain (RBD) and receptor-binding motif (RBM). This mutation increases replication and infectivity of the coronavirus, while making it more vulnerable to neutralization antibodies.
- The virus will continue to mutate till it finds a gene of importance in the RBM. All monoclonal antibodies act against RBM.
- The Nigeria mutation P681H (proline to histidine) is an isolated mutation. This mutation is present near the S1/S2 furin cleavage site, a site with high variability in coronaviruses. It has emerged spontaneously several times.
- The mutation N440K is in India (asparagine to lysine). This mutation is in the RBM and is ready

for adoption by the virus. It is found in Andhra Pradesh (34% of genomes analyzed) and also in Karnataka, Maharashtra and Telangana. One case of reinfection with this mutant strain has been reported in Noida.

- Another mutation in India has been seen in Kerala; C1240Y and P84T. It is not in the RBD or RBM and hence this mutation will die out.
- Another mutation is in Australia - S477N (serine to asparagine); this is in the RBM and so is available for adoption by the virus.
- Cluster 5 mutation from Denmark, with 69/70 deletion. Since it was an isolated strain, it died out. But, this was adopted by the UK strain.
- Diagnosis of UK variant: S gene negative and the rest are positive on current reverse transcription polymerase chain reaction (RT-PCR) test.
- The UK strain is VUI (VOC) 2020-12/01; there are 23 gene mutations. The major substitution is N501Y (asparagine (N) has been replaced with tyrosine (Y). It has three deletions - Hi 69 histidine, 70 Vi Valine and 144. Other substitutions are A570 D, D614G, P681H (near the S1/S2 furin cleavage site), T716I, S982A and D1118H.
- A recent case report of an immunocompromised individual persistently infected with SARS-CoV-2 acquired around 10 mutations in the spike protein over 154 days, notably including N501Y. This mutation was due to killing of NSP 14; this mutation was also adopted by the UK strain.
- The function of NSP 14 (part of RdRP) is proof reading. If this function is defective, then mutations will occur. NSP 14 is killed by remdesivir and favipiravir. If resistance to antiviral drugs develops, mutations will occur.
- The UK strain has an affinity to 7-11 year age group.
- The South Africa variant 501.V2; there are three mutations (two are in RBD and one in RBM). N501Y is the main substitution (enhances binding affinity to angiotensin-converting enzyme 2 [ACE2]). Other substitutions are K417N lysine with asparagine (would abolish key interactions with Class 1 Nabs and likely contributes towards immune evasion at this site) and E484K glutamic acid with lysine (enhances binding affinity to ACE2 and confers resistance to class 2 Nabs). About 90% of cases in South Africa are due to the new variant.
- The UK mutation is only a start; more mutations can be expected in the next few months. The virus will become more contagious. It may become chronic. Hence, this is the best time to take a vaccine.
- Both vaccines (vector vaccine and killed vaccine) have immunogenicity and are safe.
- There should be no controversy over the killed vaccine.
- Vector (nonreplicating) vaccine and mRNA vaccine can be given to immunocompromised persons.
- In phase 1 trial of Bharat Biotech, 3 different combinations were used based on the adjuvants; phase 2 looked at immunogenicity and used two doses of adjuvants; one had 92% efficacy and another had 98% efficacy. On this basis, the expert committee gave its recommendation for permission. Phase 3 trial is nearing completion.
- Major trials of Oxford-AstraZeneca vaccine are done in the UK; in Bharat Biotech vaccine, all phases were done in India.
- Vaccine war is inevitable, but is not the need of the hour, especially when there is so much of vaccine hesitancy.
- Both vaccines are immunogenic, both are safe.
- The focus should be on bringing the right and credible information to the people. There is a need for transparency and accountability in the system.
- Doctors should be role models and be messengers of change to remove vaccine hesitancy.

Round Table - Expert Group on Environment Zoom Meeting on "Solid Waste Management Issues in Cities – Technological Solutions for Centralized and Decentralized Waste Management"

10th January, 2020 (12 noon-1 pm)

Participants: Dr KK Aggarwal, Dr Anil Kumar, Mr Dipankar Saha, Dr SK Tyagi, Dr UK Priyadarshi, Mr Pradeep Khandelwal, Mr Neeraj Tyagi, Dr Suresh Mittal, Dr Rahul Sengar, Ms Ira Gupta, Dr S Sharma

The meeting was chaired by Mr SK Tyagi

Key points from the discussion

- There are several challenges and issues of concern in management of solid waste.
- Solid waste is the major cause of air, water and land pollution.
- According to 2016 data, cities all over the world generated 2.01 billion tonnes of solid waste; this waste generation is expected to increase to 3.40 billion tonnes by 2050.

- India is the third largest producer of municipal solid waste after China and US.
- According to Ministry of Housing and Urban Affairs, as of January 2020, 147,613 metric tonnes of solid waste is generated per day in India.
- A report published in 2014 by Task Force of the Planning Commission suggested that urban India will generate 2,76,342 tonnes per day of waste by 2021 and 11,95,000 tonnes per day by 2050.
- Transport is a challenge in the urban areas because of the huge amounts of solid waste produced; financial constraints and political will are other challenges.
- Segregation of waste at source in coded bins (blue for dry waste, green for wet waste) is mandatory in the 2016 solid waste management rules.
- About 52% of biodegradable waste can be managed in decentralized manner, if it is properly segregated.
- Solid waste is a mixed type of waste and includes domestic waste, commercial waste, institutional waste and sometimes biomedical waste (although this is to be managed separately as per biomedical waste management rules 2016, amended in 2018, 2019 and July 2020).
- More than 60% of solid waste can be minimized by proper segregation, collection and disposal. Paper and paper-related products constitute 38% of solid waste (can be recycled); yard waste constitutes 13-14%, food waste 10-11% (reduced by composting), plastic waste (can be recycled), metals 8% (can be recycled), glass and ceramics 6% (can be recycled) and wood 5% (can be reused).
- Composting, manuring, gasification, pyrolysis and waste-to-energy are well-established technologies. In India, the focus should be on gasification and waste to energy.
- Landfill should be arranged in a scientific manner with provisions of proper collection of leachate along with other layers, to prevent contamination of ground water.
- There is lack of awareness about the solid waste management rules. These rules have fixed duties of the waste generator, local bodies and regulatory authorities.
- Individual waste generators are required to segregate waste at their level, which is to be collected by the local bodies for processing.
- Bulk waste generators and industrial waste generators are required to segregate waste at their level and process it. This is almost negligible today.
- Dry waste is of two types - combustible and recyclable. Wet waste includes food, fruits, vegetables; these can be recycled by home/community composting or bio-mechanization; if this is not possible then centralized management can be done: Composting or bio-mechanization for wet waste; dry waste can be recycled or waste-to-energy and inert waste (dust, construction and demolition debris [recyclable products]).
- Waste has to be minimized. Everybody should adopt the principles of reduce, recycle and reuse.
- Delhi has 50 decentralized plants; there are 3 waste-to-energy plants and 2 more will be started; there are 4 construction demolition plants working and 2 more will start.
- Solid waste is generated by us and this problem has to be solved by us.
- Until there is a participatory approach, solid waste management would not be successful.
- Citizens have to cooperate so that municipal bodies can manage it.
- Behavioral change is a must for sustainable waste management.
- Segregation at source is the best solution. Once the waste is segregated, it becomes manageable.
- There is a need for simple cost-effective methods on how to reuse waste and recycle waste products.
- RWAs have an important role in solid waste management.
- All persons aged 50 years and above should register themselves for the vaccine and take vaccine at the earliest.

Circadian Rhythm and COVID-19: Possible Explanations of Post-COVID Symptoms

Misalignment of the circadian timekeeping system with the desired sleep schedule or impairment of the circadian modulation of sleep and wakefulness often leads to clinically significant symptoms of insomnia and excessive daytime sleepiness, besides impaired physical, neurocognitive, emotional and social functioning.

Types

Disrupted sleep-wake pattern: Characterized by abnormalities in the sleep-wake pattern compared with those of most healthy adults under similar environmental conditions.

- **Delayed sleep-wake phase disorder:** The circadian system aids wakefulness until late in the evening, giving way to **delayed sleep onset, typically occurring at midnight or later.** If sleep is attempted at an earlier desired bedtime, sleep onset insomnia will occur. In the morning, the circadian system actively drives sleep later than conventional or desired wake-up times. If left undisturbed, such as on weekends or vacation, patients sleep well into the morning, sometimes until noon or later. When conventional rise times are required depending on school or work, patients with delayed sleep-wake phase disorder find it very difficult to wake up and feel alert.
- **Advanced sleep-wake phase disorder:** Patients become sleepy earlier in the evening compared to conventional or desired bedtimes, and wake up earlier in the morning and cannot go back to sleep. This pattern of phase advancement is seen physiologically with aging but is more marked in patients with pathologic phase advance. When patients force themselves to stay awake in the evening, they wake up early and thus accumulate sleep debt.
- **Non-24-hour sleep-wake rhythm disorder:** Patients have a free-running circadian system, which is often longer than 24 hours. There are periods when the circadian system actively drives wake during the night-time, causing insomnia and actively drives sleep during the daytime, causing excessive daytime sleepiness. As the clock continues to free run, there are periods of proper alignment, with temporary resolution of the sleep-wake disturbances. Alternatively, patients may simply go to bed later and later on every subsequent night.
- **Irregular sleep-wake rhythm disorder:** The circadian system fails to consolidate periods of wakefulness and periods of sleep. This leads to multiple short sleep episodes spread across the 24-hour day, interspersed with multiple periods of wakefulness.
- **Jet lag disorder:** People find it difficult to fall asleep or maintain sleep at night after air travel across two or more time zones. Excessive daytime sleepiness may also occurs on account of reduced total sleep time as well as circadian misalignment. The disturbances continue until the circadian system adjusts to the new light-dark cycle at the destination.
- **Shift work disorder:** It manifests as difficulty with sleep or wakefulness at times that are imposed by shifts running counter to the light-dark cycle. Patients accumulate sleep debt and have increased risk for accidents, errors and other adverse health outcomes.

F**unctional impairment:** As seen in any sleep disorder resulting in inadequate duration or quality of sleep, patients tend to **experience impaired functioning in the workplace, at home, or in school, which appears to occur as a result of suboptimal neurobehavioral functioning in domains of concentration, memory and processing speed.** Physical fatigue may also contribute to impairment. Mood disturbances may also accompany circadian disorders. Comorbid depression is well recognized in association with delayed sleep-wake phase disorder. (https://new.uptomed.ir/)

The suprachiasmatic nucleus (SCN) in the hypothalamus is often referred to as the master biological clock or pacemaker. This generates and synchronizes internal circadian rhythms with external time cues such as light, and helps control multiple circadian rhythms, such as daily fluctuations in core body temperature, as well as melatonin secretion by the pineal gland. Bright light can shift the timing of circadian rhythms.

Light just before the temperature minimum will typically shift the temperature minimum clockwise to a later time (phase delay). Light soon after the temperature minimum will shift the temperature minimum counter-clockwise to an earlier time (phase advance). The timing of the light relative to the temperature minimum will determine how much the circadian rhythms shift.

Darkness generally has the opposite effect of light upon circadian rhythms. Darkness in the morning will cause a phase delay in the rhythms; darkness in the evening will cause a phase advance in the rhythms.

A case for melatonin

- Melatonin secretion manifests a similar circadian rhythm, with plasma and urine concentrations low during daylight, rising after the onset of darkness, peaks in the middle of the night between 11 pm and 3 am, and falling sharply before the time of light onset.
- While this rhythm normally is tightly entrained to the environmental light cycle, it does persist when people are placed for a few days in a dark room. It does not immediately phase shift when the light schedule is altered, thus suggesting that it is not simply generated by the light-dark cycle but also by cyclic endogenous signals, probably

arising in the SCN. Signals that originate in the retina or the SCN reach the pineal gland through a retinohypothalamic tract, the superior cervical ganglia and postganglionic sympathetic fibers that re-enter the cranial cavity. Light has no known direct effects on pineal melatonin synthesis in humans and other mammals.

- **The potential of exogenous melatonin to synchronize and to shift the phases of various human circadian rhythms is generally accepted.**
- In studies with healthy volunteers, **0.5 mg of pure melatonin** or 0.05 mg of melatonin in corn oil **(which leads to earlier peaks in, and the more rapid disappearance of, elevated plasma melatonin concentrations)** could advance the onset of nocturnal melatonin secretion **when administered at 5 pm, and larger doses led to greater phase advances. [*uptodate.com*]**

Furthermore, melatonin was able to shift the core body temperature rhythm. But a statistically significant effect was found only with doses ≥0.5 mg. These doses raised plasma melatonin concentrations well above the upper limits of normal (>1327 pg/mL [5712 pmol/L]), suggesting that this may not be a physiologic effect. (*Brain Res. 1995;688(1-2):77.*)

Caution: Don't take melatonin right before bed because it takes several hours for it to become effective.

If you normally stay up past midnight, but would like to nod off around 11 pm, take melatonin at 6 pm.

Conversely, if you go to bed at 8 pm and rise at 4 am, it's better to take melatonin in the late morning or early afternoon.

Comments: Biological clock is disturbed in COVID; thermo dysregulation is seen; melatonin may be the answer, given at 5 pm.

Metformin Use is Associated with Reduced Mortality in COVID-19 Diabetics

Diabetes is an independent risk factor for COVID-19-related mortality; however, the risk is reported to be considerably reduced in patients taking metformin before the diagnosis of COVID-19. This raises the possibility that metformin may be protective in this high-risk population, suggest findings published in *Frontiers in Endocrinology*.

The study noted that metformin use prior to the diagnosis of COVID-19 was linked with nearly 3-fold reduction in mortality and significantly lower unadjusted and adjusted odds ratios in subjects with diabetes. The effect persisted even after correcting for age, sex, race, obesity and hypertension or chronic kidney disease and heart failure. The mechanisms through which metformin might improve prognosis in COVID-19 go beyond any expected improvement in glycemic control or obesity as blood glucose, hemoglobin A1c, or body mass index (BMI) were not lower in COVID-19 survivors on metformin.

Investigators retrospectively analyzed electronic health records of 25,326 individuals tested for COVID-19 from February 25 to June 22, 2020 at the University of Alabama at Birmingham Hospital. The primary outcome was mortality in COVID-19-positive patients. A total of 604 individuals had a confirmed positive COVID-19 test and 239 (39.6%) had diabetes. In all, 67 (11%) deaths were reported. Age of 50 and above, male sex and hypertension were found to be associated with a significantly raised risk of death. Diabetes was associated with a "dramatic" increase in mortality and was an independent risk factor even after correcting for age, race, sex, obesity and hypertension. Of the deaths reported, 67% occurred in patients with diabetes.

Looking into the effects of diabetes treatment on adverse COVID-19 outcome, researchers noted that prior metformin use significantly reduced the odds of dying while prior insulin use was not found to affect mortality risk. The mortality rate of 11% among patients taking metformin was comparable to that of the general COVID-19-positive population and was considerably lower than the 24% mortality rate observed in patients with diabetes not taking metformin. Metformin treatment prior to diagnosis of COVID-19 was thus found to have an independent association with a significant reduction in mortality in patients with diabetes and COVID-19. *(Source: DG Alerts*)

High-titer Plasma Reduces Mortality Risk in Nonventilated Hospitalized COVID-19 Patients

Among hospitalized COVID-19 patients not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was found to be associated with a lower risk of death compared to transfusion of plasma with lower antibody levels in a study published in *The New England Journal of Medicine*.

Patients who were administered plasma within 3 days after a diagnosis of COVID-19 had a lower risk of death in comparison with those who received transfusion later during the disease course.

This retrospective study included 3,082 patients hospitalized with COVID-19 from 680 acute care

facilities across the US. Overall, 61% of the patients were men, and 69% were below 70 years of age. The cohort was stratified into three groups depending on anti-SARS-CoV-2 IgG antibody levels based on signal-to-cut off ratios: low (<4.62), medium (4.62 to 18.45), or high (>18.45). Patients in the three groups were generally similar in terms of demographic characteristics, risk factors associated with severe COVID-19, and concomitant use of therapeutic agents for COVID-19. The primary outcome was death within 30 days following transfusion of convalescent plasma.

Death within 30 days after plasma transfusion was reported in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2,006 patients (27.4%) in the medium-titer group and 166 of 561 patients (29.6%) in the low-titer group. Patients in the high-titer group had a lower relative risk of death within 30 days after transfusion compared to those in the low-titer group (relative risk [RR], 0.75; 95% confidence interval [CI], 0.61-0.93). Additional analyses with adjustment for patient demographic characteristics (age, weight status, and race) and clinical characteristics (receipt of invasive mechanical ventilation, use of concomitant therapeutics, and hypoxemia) exhibited a similar association.

Among patients who were not receiving mechanical ventilation, death within 30 days after plasma transfusion occurred in 22.2% in the low-titer group, 19.4% in the medium-titer group and 14.2% in the high-titer group. Among patients who were receiving mechanical ventilation, death within 30 days following plasma transfusion was reported in 43.7% in the low-titer group, 41.6% in the medium-titer group and 40.5% in the high-titer group.

In the fully adjusted RR regression model, the lower risk of death within 30 days after plasma transfusion in the high-titer group was evident among patients who were not receiving mechanical ventilation before transfusion (RR, 0.66; 95% CI, 0.48-0.91). There appeared to be no effect on mortality among patients who received mechanical ventilation prior to transfusion (RR, 1.02; 95% CI, 0.78-1.32).

The unadjusted mortality within 30 days following transfusion was lower among patients who received a transfusion within 3 days after receiving a diagnosis of COVID-19 (point estimate, 22.2%; 95% CI, 19.9-24.8) compared to those who received a transfusion 4 or more days after the diagnosis of COVID-19 (point estimate, 29.5%; 95% CI, 27.6-31.6). (*Source: DG Alerts*)

Ad26.COV2.S Vaccine

Next in line in the armamentarium against COVID-19 is likely the single-dose Ad26.COV2.S vaccine, being developed by Johnson & Johnson/Janssen, anticipate infectious disease experts.

It got closer with promising interim phase 1/2a trial results that were published online January 13 in *The New England Journal of Medicine*.

A single Ad26.COV2.S dose was found to be associated with S-binding and neutralizing antibodies in over 90% of the participants. The finding was evident in both adults aged 18-55 years and participants 65 years and older, as well as in participants given low-dose or high-dose vaccinations.

The results also pointed to a durable vaccine response.

The take-home message is a high neutralizing antibody responder rate to a single dose of the Ad26.COV2.S COVID-19 vaccine candidate. These responses and antibody titers are stable for at least 71 days.

Another advantage is the need of less stringent storage requirements - only regular refrigeration vs a need to freeze the Pfizer/BioNTech and Moderna vaccines.

The Ad26.COV2.S vaccine can be refrigerated for up to 3 months at 2°-8 °C.

Johnson & Johnson vaccine is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike (S) protein.

The urgency of the COVID-19 pandemic hastened the vaccine development process; therefore, preclinical trials were conducted simultaneously and not sequentially. The rollout is expected in March.

The phase 1/2a multicenter, randomized, double-blind and placebo-controlled trial interim results are highly encouraging and support the single inoculation approach. It shows solid antibody, CD4 T-cell, and CD8 T-cell responses.

At baseline for the phase 1/2a trial, 2% of the younger group and 1% of the 65+ group were seropositive for SARS-CoV-2 S-specific antibodies.

Overall, 402 people in the younger age cohort and 403 in the 65 and older group were given a first dose of the Johnson & Johnson vaccine. Many participants also received a second dose after a gap of 56 days for a separate trial, ENSEMBLE2, which compares safety and efficacy between single- and double-dose regimens.

A single dose was shown to be associated with a higher incidence of solicited systemic adverse events in the higher vaccine dose group. Grade 3 adverse events decreased with increasing age.

Injection site pain on the day of immunization or the next day was the commonest local reaction. The pain generally resolved within 24 hours. Fever was reported by 15% in the low-dose vaccine group and 39% in the high-dose group. The most common Grade 1 or 2 solicited systemic adverse events reported included fatigue, headache and myalgia.

There were five serious adverse events, including four that were deemed not related to vaccination: hypotension, bilateral nephrolithiasis, legionella pneumonia and one case of worsening of multiple sclerosis. The vaccine-related serious adverse event was a fever that led to hospitalization because of suspicion of COVID-19. The patient recovered within 12 hours. (*Source: Medscape*)

HCFI Round Table Expert Zoom Meeting on "COVID-19 Vaccine – Indications and Contraindications"

16th January, 2021 (11 am-12 pm)

Participants: Dr KK Aggarwal, Dr Anita Chakravarti, Prof Mahesh Verma, Mr Bejon Misra, Ms Upasana Arora, Dr KK Kalra, Dr Suresh Mittal, Ms Ira Gupta, Dr S Sharma

Consensus Statement of HCFI Expert Round Table

- Two vaccines – Covishield and Covaxin have been approved based on the recommendation of the Expert group.
- The Health Ministry has issued guidelines regarding precautions and contraindications for COVID vaccine.
- The COVID-19 vaccine is approved (EUA) for 18 years and above. Co-administration of other vaccines is not allowed (there should be a gap of at least 14 days). Interchangeability of COVID vaccine is not permitted. Many questions need to be answered such as if a person develops anaphylaxis to one vaccine, can he be given the other vaccine? What about persons younger than 18 years with comorbidities?
- The vaccine is contraindicated in persons with history of allergies and anaphylaxis to a previous dose of vaccine, any vaccine, drugs and food allergy. This means that at least 10% of the population with history of allergies will be out of the vaccine indications.
- Temporary contraindications (vaccination deferred for 4-8 weeks after recovery) include persons having active symptoms of SARS-CoV-2 infection. But this does not define the symptoms or the duration of symptoms. Another temporary contraindication is "acutely unwell and hospitalized patients due to any illness", which also needs to be clarified.
- As per a newspaper report, persons who suffer any adverse reaction to the vaccine will be given compensation. But the amount of compensation has not been clarified.
- There is an allergic response to the vaccine along with viral response, inflammatory response and thrombotic response.
- Norway has reported deaths of elderly frail individuals following COVID vaccination (Pfizer mRNA vaccine).
- mRNA is known to be inflammatory. Killed vaccine is known to be safe for elderly, frail and those with comorbid conditions.
- All those who have natural risk factors for natural virus infection (e.g., uncontrolled diabetes) may develop mild inflammatory reactions after vaccine, which they cannot tolerate.
- Reactions caused by mRNA vaccine are not necessarily caused by mRNA. The other components used such as nanoparticles, polyethylene glycol (PEG) may be responsible.
- Inactivated vaccines are safe.
- Assess the person, especially the elderly, before vaccination. After vaccination, anticipate and treat mild inflammatory reaction. Check for rise in C-reactive protein (CRP).
- High CRP on Day 0 means proinflammatory and prothrombotic state; start anticoagulants. Give steroids if any signs of cytokine release on Day 3.
- All precautions to be taken should be in place at the vaccination center and all citizens should be made aware of these precautions.
- If you take the vaccine, assess your expected response. There is likely to be a foreign body local response (redness, pain, fever on Day 1), which is a typical response to a viral protein.
- If the virus is replicative, there is Th1 response by Day 2, which disappears by Day 7, i.e., lymphocytes should become normal. By Day 4, CRP should become normal.

- Exaggerated inflammatory response means rise in CRP and ferritin. If there is a sudden rise in CRP after vaccination, do not wait for symptoms to develop, especially in elderly fragile people and/or persons with comorbid conditions.
- For Covishield AEFI, the Health Ministry has mentioned that "very rare events of demyelinating disorders have been reported following vaccination with this vaccine without the casual relationship establishment". It should be given with caution to individuals with thrombocytopenia.
- Interim results of a phase 1-2a trial of Ad26.COV2.S COVID-19 vaccine published in the *New England Journal of Medicine* show that the inflammatory response (CD4 -Th1 and CD8 - Th2) comes on Day 15.
- Serial CRP measurements should be done following COVID vaccination. If CRP is rising, this may suggest an inflammatory response. More studies are required to validate this hypothesis.

What is Known About the Vaccines' Short-term Safety?

- Rare events will be reported, which will escalate the attention and worry that will be disproportionate to the actual risk. It will be important to put these rare events into perspective, highlighting the fact that these risks are considerably lower than the risk of getting sick with COVID-19.
- Both the mRNA vaccines are classified as reactogenic. This means that there will be some side effects in most people who will be vaccinated, which represent the quick immune response generated by these vaccines. **These vaccines should be put in the same side-effect category as the recombinant shingles vaccine (Shingrix)**.
- The most common side effect is pain at the injection site, particularly in the first 24 hours following administration. About 1% of individuals in the trials reported the pain to be severe. Other relatively common side effects include fatigue and headache. High fevers are less commonly seen. These side effects often resolve within a few days and respond to acetaminophen or a nonsteroidal anti-inflammatory drug (NSAIDs), like ibuprofen. Side effects appear to be more common in the younger recipients compared to the older subjects, and the second shot tends to induce more side effects versus the first one.
- Bell's palsy was more often reported among vaccine recipients compared to controls. However, the number of cases was not large enough to suggest that this was beyond the number that is naturally seen in populations of this size by chance.
- No cases of Guillain-Barré syndrome or transverse myelitis were observed.
- Hypersensitivity was noted equally in the placebo and vaccine groups in both the trials. However, following the distribution of the vaccines in the United Kingdom and the United States, there were reports of severe allergic reactions (anaphylaxis) soon after the first dose.
- The major suspect behind these reactions appears to be polyethylene glycol. This compound is present in both the vaccines. Owing to these rare events, administration of the vaccines is followed by a period of 15 minutes of observation. The duration is 30 minutes for those who have a history of severe allergic reactions of any kind.
- These allergic reactions are uncommon, and it is estimated that anaphylaxis will occur at about 1 in 1,00,000 doses.
- This rate is higher than what is seen with other vaccines, but considerably lower than the rate reported with penicillin (1 in 5,000).
- As the vaccine is injected, the mRNA is taken up by the macrophages near the injection site. The spike protein appears on the surface of the macrophages, and incites an immune response that provides protection against natural infection with SARS-CoV-2.
- Enzymes subsequently degrade and dispose of the mRNA. There is no live virus, and no genetic material enters the nucleus of the cells.
- It is indeed brilliant how the insight put mRNA inside a lipid coating to prevent it from degradation. (*Source: NEJM*)

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72nd Annual Cardiology Conference

CARDIOVASCULAR SAFETY OF SULFONYLUREAS: IT'S A LONG JOURNEY TILL CAROLINA

Dr Manish Bansal, Gurugram

- Although still more evidence is needed, it appears that modern sulfonylureas (SUs) may not be associated with cardiovascular (CV) harm.
- When affordability is not an issue, sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA) are preferred in patients at high CV/heart failure risk.
- However, if the cost is an issue, modern SUs are a reasonable alternative.
- CV safety of SUs: It's a long journey till CAROLINA.

RIVAROXABAN: A NEW TREATMENT PARADIGM IN THE SETTING OF VASCULAR PROTECTION?

Dr KP Pramod Kumar, Chennai

The pathophysiology of atherosclerosis involves a diseased endothelium, lipid accumulation and low-grade inflammation. Later stages of coronary artery disease (CAD) and peripheral artery disease (PAD) are characterized by atherothrombosis induced by plaque rupture, caused by fibrin formation and platelet activation, resulting in vessel occlusion, followed by organ damage, such as myocardial infarction (MI), stroke or limb ischemia. The high disease burden associated with CAD and PAD necessitates the need for continuous vascular protection beyond the treatments available at present, including antiplatelet agents.

The factor Xa plays a key role in the etiopathogenesis of atherothrombosis. Experimental data point to the anti-inflammatory and antioxidative potential of rivaroxaban, and also suggest that the drug may improve endothelial dysfunction. The COMPASS trial revealed that in patients with stable atherosclerotic vascular disease, adding rivaroxaban 2.5 mg twice daily (vascular dose) to aspirin yielded a higher cardiovascular protection compared to aspirin alone.

The ROCKET-AF trial noted that in comparison with warfarin, rivaroxaban 20 mg once daily (15 mg if moderate renal dysfunction) (anticoagulant dose) was at least as effective as warfarin for preventing stroke or systemic embolism among patients with nonvalvular atrial fibrillation, with a trend toward a reduction in the risk of cardiovascular outcomes. Rivaroxaban, therefore, might have a vascular protective effect beyond its stroke/systemic embolism preventive activity.

Suggested Reading: [1]Barrios V, Almendro-Delia M, Facila L, et al. Rivaroxaban: Searching the integral vascular protection. Expert Rev Clin Pharmacol. 2018;11(7):719-28. [2]Bauersachs R, Zannad F. Rivaroxaban: A new treatment paradigm in the setting of vascular protection? Thromb Haemost. 2018;118(S 01):S12-S22.

CLINICAL EVALUATION IS ENOUGH TO ASSESS DECONGESTION AND DECIDE ON DISCHARGE IN HEART FAILURE

Dr Ajay Bahl, Chandigarh

- Clinical assessment based on symptoms like edema, breathlessness and orthopnea, weight records, jugular venous pressure, third heart sound on auscultation, and renal function tests should be used to guide therapy and decision on discharging patients with acute decompensated heart failure.
- Natriuretic peptides are useful in the diagnosis and prognostication of acute heart failure.
- However, guided therapy based on natriuretic peptide levels has not been shown to reduce post-discharge clinical events.

ASYMPTOMATIC TO SYMPTOMATIC HEART FAILURE – PREDICTORS OF PROGRESSION

Dr Harikrishnan S, Trivandrum

Progression from Stage A/B of heart failure to Stage C/D should be prevented or delayed to improve the outcomes. Close periodic monitoring is needed. Clinical markers are not very sensitive and specific. We need to use biomarkers like B-type natriuretic peptide (BNP)/N-terminal (NT)-proBNP.

Echocardiographic parameter ejection fraction may not be that sensitive, so parameters like GLS (global longitudinal strain) is found to be very useful. Control of risk factors is the key. BP should be controlled to the level of 130/70-80 mmHg, considering the reverse J curve phenomenon.

Diabetes should be controlled to glycated hemoglobin (HbA1c) levels of 7-8%. Early initiation of

renin-angiotensin-aldosterone system (RAAS) blockers, β-blockers and aldosterone blockers may help. SGLT2 inhibitors may be useful; the data is emerging.

WHO BENEFITS FROM TAKING A STATIN, AND WHEN?

Dr BKS Sastry, Hyderabad

The beneficial effects of statins are attributed to their capacity to decrease cholesterol biosynthesis, particularly in the liver, where they are selectively distributed, and to the modulation of lipid metabolism, derived from their inhibition of HMG-CoA reductase. Statins are known to have antiatherosclerotic effects that are positively correlated with the percent reduction in low-density lipoprotein (LDL) cholesterol. Statins also exert antiatherosclerotic effects independently of their hypolipidemic action, which are referred to as their pleiotropic effects.

Guidelines from the US Preventive Services Task Force, American College of Cardiology and American Heart Association suggest four main groups of people who may obtain benefits from the use of statins:

- **Individuals who don't have heart or blood vessel disease, but have one or more cardiovascular disease (CVD) risk factors and a predicted 10-year risk of a heart attack >10%.** People with diabetes, high cholesterol or high blood pressure, or who smoke and whose 10-year risk of a heart attack is >10% constitute this group.
- **People who have CVD related to hardening of the arteries.** This group includes individuals who have had heart attacks, strokes due to blockages in a blood vessel, ministrokes (transient ischemic attacks), PAD or have undergone surgery to open or replace coronary arteries.
- **Individuals with very high LDL cholesterol.** This group includes adults with LDL cholesterol levels of 190 mg/dL (4.92 mmol/L) or higher.
- **People with diabetes.** This group includes adults aged 40-75 years who have diabetes and LDL cholesterol level of 70-189 mg/dL (1.8 and 4.9 mmol/L), particularly if there is evidence of blood vessel disease or other risk factors for heart disease, such as high blood pressure or smoking.

The US Preventive Services Task Force recommends low- to moderate-dose statins in adults 40-75 years of age, having one or more risk factors for heart and blood vessel disease and at least a 1 in 10 likelihood of having a CVD event in the ensuing 10 years.

Suggested Reading: [1]Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001;5(4):378-87. [2]Available from: https://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/statins/art-20045772.

DAPA-HF, EMPEROR-REDUCED AND DAPA-CKD: PUTTING IT ALL TOGETHER

Dr John JV McMurray, Glasgow

SGLT2 inhibitors are much more than just effective glucose-lowering therapy for T2D *(think angiotensin-converting enzyme [ACE] inhibitor or statin!).* They reduce the risk of developing heart failure in patients with T2D and chronic kidney disease (CKD) patients (even CKD patients without T2D). They reduce the risk of hospitalization and death in patients with heart failure and reduced ejection fraction, with and without diabetes – and improve symptoms/health-related quality of life. They reduce the rate of decline in estimated glomerular filtration rate (eGFR) in patients with heart failure with reduced ejection fraction (HFrEF) and the risk of end-stage kidney disease (ESKD) in patients with CKD, with and without diabetes. SGLT2 inhibitors protect the heart and kidneys and have become the new "standard of care" in HFrEF and CKD.

CORONARY ARTERY CALCIUM – WHAT LIES BENEATH?

Dr Mona Bhatia, New Delhi

Coronary artery calcium (CAC) is ready for prime time – A strong predictor of CV risk; Cost-effective, safe, widely available. Fully endorsed in the guidelines. Integrates well into our current healthcare landscape to focus on prevention and shared decision-making. CAC is recommended when the individuals' atherosclerotic cardiovascular disease (ASCVD) 10-year risk is uncertain (5-7.5% odds ratio [OR] 7.5 -20%). CAC is a companion diagnostic, helps accurately identify responders, reduce the number needed to treat, with efficient use of scarce resources. Particularly useful in patients who are statin reluctant or statin intolerant. Aids decision for nonstatin/aspirin therapy.

KETO DIET – IS IT SAFE FOR THE HEART?

Dr BRJ Kannan, Madurai

Dietary fat has been projected as a villain in the past 60 years or so. This has led to an increase in the carbohydrate intake to the tune of more than 75% of daily calories. Any diet with a carb content higher than 55-60% of daily calories would increase mortality. Keto diet, a very high-fat diet with <30% calories from carbohydrates, is unsafe for the heart. Any diet with

a carbohydrate content of lesser than 40% of daily calories also would increase mortality. For the best CV outcome, we need to balance the diet by increasing the current fat intake to at least 25% of daily calories with a corresponding reduction of carbohydrates to 50-55%.

CARDIOVASCULAR IMPACT OF COVID-19: AN AMERICAN PERSPECTIVE

Dr Mark Huffman, Chicago

- COVID-19 in the US: The problems – Lack of coordination across and within states; Slow reporting of facility-based data to identify and respond to health disparities; Catastrophic health spending; Political polarization, misinformation, widespread distrust.
- The US has the largest burden of diagnosed COVID-19, accounting for 22% of global cases, and will likely have the largest burden of COVID-19 complications, including HF.
- The pandemic exposed the US's fragile and inequitable health system arrangements and under-investments in public health.
- The heart and soul of the US have been battered in 2020; a renewed spirit of cooperation, collectivism and humility are needed, as well as safe, effective and equitably-distributed vaccines.

MANAGING A CVD PATIENT – FROM PRIMARY TO SECONDARY PREVENTION

Dr Peter Lin, Canada

- JUPITER Trial – It was conducted in low-risk patients; patients with (LDL) cholesterol levels of <130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/L or higher were included.
- The trial was stopped after a median follow-up of 1.9 years. There was a 44% reduction in primary endpoint, 54% reduction in MI, 48% reduction in stroke, 46% reduction in revascularization and 20% reduction in death with rosuvastatin therapy.
- HOPE 3 study – It included intermediate risk patients. First co-primary endpoint: Composite of CV death/MI/stroke for rosuvastatin vs. placebo: 3.7% vs. 4.8%, hazard ratio (HR) 0.76, number needed to treat (NNT) = 91. There was no difference in incidence of diabetes in the two groups in the HOPE 3 trial (New-onset diabetes mellitus: 3.9% vs. 3.8%, p = 0.82).
- REDUCE-IT randomized patients to receive icosapent ethyl twice daily or placebo. A primary endpoint event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group, an absolute between-group difference of 4.8% points; the NNT to avoid one primary endpoint event was 21 (95% CI, 15-33) over a median follow-up of 4.9 years.
- Statins should form a good baseline therapy. Drugs like ezetimibe can be added later.
- Studies from the Netherlands, UK and Canada suggest that rosuvastatin is associated with lower incidence of fatal and nonfatal CVD, compared to other statins and there was no evidence of greater risk of myopathy, rhabdomyolysis, acute renal failure and acute liver injury among patients treated with rosuvastatin compared to other statins.

A GLIMPSE INTO THE 70 YEARS LEGACY OF FRAMINGHAM HEART STUDY

Dr Rakesh Yadav, New Delhi

Framingham Heart Study (FHS) has been one of the most important studies for CV health worldwide. It has firmly established various risk factors (hypertension, dyslipidemia, smoking and diabetes) for CVD, heart failure, stroke etc., and paved the path for various randomized, controlled clinical trials that led to the subsequent development and implementation of effective treatments for these conditions. With the USA's changing demographics, changing epidemiology of CV, and the formation of so-called mega-cohorts, the role of FHS has changed over the past 70 years and has maintained its importance in this regard. It remains a lodestar for epidemiological cohort studies for CVD – To understand the trends in risk factors and disease and understand what can be done to lower the risk and burden of CVD. It has also been and will continue to be an important institution to train CVD epidemiologists, biostatisticians and bioinformaticians (FHS has trained >90 fellows over the past three decades). An increasing amount of data from various cohorts is currently being made available via major data repositories, making access to data by investigators not formally affiliated with the FHS much easier. FHS has maintained its legacy even after 70 years of completion.

CARDIOVASCULAR IMPACT OF COVID-19: EUROPEAN EXPERIENCE

Dr Barbara Cassedei, England

- The European response to COVID-19 has been slow and inhomogeneous. This has cost many lives.

- Evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes acute myocarditis is largely absent.
- Interrogation of continuous patient registries and large data sources (e.g., UK Biobank, openSafely, SwedeHeart, NICOR) and digitized health systems have accurately highlighted the disparities in risk and outcomes of COVID-19 and provided the infrastructure for undertaking pragmatic randomized controlled trials.
- Once corrected for age, diabetes, obesity and social deprivation, the excess risk of coronavirus disease 2019 (COVID-19) death conferred by CVD is relatively small. The impact of the pandemic on non-COVID-19 mortality has been significant. This may have contributed to the excess non-COVID-19-related mortality observed during the first wave of the pandemic

LDL-C MANAGEMENT: TARGET-BASED OR DOSE-BASED?

Dr Sadanand Shetty, Mumbai

I will continue with high-dose statin irrespective of low LDL cholesterol.

Why is longer therapy with high-intensity statin required?

- Longer the better: Takes time for complete clinical benefit from the time of LDL-lowering.
- Lowest LDL levels are best: No safety concerns with low LDL levels.
- The incremental benefit with absolute LDL reduction: Reduce residual risk.

I WILL NOT RECOMMEND ABPM ROUTINELY

Prof (Dr) Vitull K Gupta, Bathinda

- Hypertension is one of the most prevalent CVD risk factors. Accurately measuring BP is essential for proper diagnosis and management.
- Recent guidelines recommend that the diagnosis of hypertension (HTN) should be based on repeated office BP measurements or ambulatory BP monitoring (ABPM) if economically feasible.
- Evidence substantiates the value of ABPM and home BP monitoring (HBPM) but does not recommend universal use of ABPM for diagnosis and management of HTN.

So, I will not recommend ABPM to all the patients routinely because of the paucity of available resources, both human and financial, and guidelines do not suggest universal use of ABPM.

ACUTE CORONARY SYNDROME

Prof (Dr) PS Banerjee, Kolkata

- Acute coronary syndrome (ACS) is a potentially life-threatening condition that affects millions of individuals each year.
- Diagnosis is based on serial ECG and cardiac marker levels, particularly using new, highly sensitive troponin T estimation.
- Initial ACS management should include risk stratification, appropriate pharmacologic management including dual antiplatelet therapy, anticoagulation and appropriate adjuvant therapies and a decision to pursue early invasive or conventional treatment strategy.
- Long-term management following an ACS event should follow evidence-based recommendations and should be individualized to each patient.

EGGS AND CARDIOVASCULAR HEALTH

Dr S Sivasankaran, Thiruvananthapuram

Egg yolk rich in cholesterol should be avoided in the diet to ensure vascular health. Cholesterol is unique to the animal kingdom and is insoluble in water. It is a crucial component of the cell membrane and steroid hormones. All cells synthesize adequate cholesterol. Dietary cholesterol reaches the cells via transport proteins and receptors. Downregulation of receptors allows cholesterol in the transport protein LDL to remain in circulation for longer, which can turn out to be vasculotoxic. Keeping LDL (a protein that transports cholesterol) below 70 mg/dL is ideal to preserve vascular health. Therefore, avoiding egg yolk in the diet is a key dietary prevention strategy for Indians at high risk for vascular disorders and diabetes.

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News and Views

Commonly Used BP Medications Safe for COVID-19 Patients: Study

Medications to treat high blood pressure (BP) did not impact the outcomes among hospitalized coronavirus disease 2019 (COVID-19) patients, noted an international team of researchers.

The study is the first randomized controlled trial to show that there is no risk for patients that continue to take these medications while hospitalized for COVID-19. As part of the REPLACE COVID trial, researchers investigated if angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) could help check complications or lead to more severe symptoms. A global rank score was developed to classify patient outcomes on the basis of four factors: time to death, length of time supported by mechanical ventilation or extracorporeal membrane oxygenation (ECMO), length of time on renal replacement therapy, and a modified sequential organ failure assessment score. Analyzing the patient outcome data, researchers noted that discontinuation of ACE inhibitors and ARBs compared with continuation of these medications had no effect on the global rank score. The findings are published in *The Lancet Respiratory Medicine*… (*HT – ANI*)

Hospitalization Risk Four-fold Higher in Blacks with T1D, COVID-19

Among type 1 diabetes (T1D) patients who contract COVID-19, Black individuals were found to be four times more likely than Whites to be hospitalized with diabetic ketoacidosis (DKA), revealed new research.

The findings come from 180 patients at 52 T1D Exchange clinical network sites. Adjusting for health insurance status and other potential confounders, the difference in DKA rates in COVID-19 appeared to be four times higher in Black compared to White patients with T1D. Hispanic patients with T1D had DKA risk which was double that of Whites, but the difference didn't achieve statistical significance. The findings were published online January 7 in the *Journal of Clinical Endocrinology & Metabolism*… (*Medscape*)

Coagulopathy Testing Tied to Better COVID-19 Outcomes

Antithrombotic prophylaxis for patients hospitalized with COVID-19 tailored by thromboelastography (TEG) findings on coagulopathy was found to be linked with better outcomes, reported a single-center study.

Among 100 COVID-19 patients who got TEG with a platelet mapping (TEG-PM) assay on admission at a center where it was routine for hypoxemic patients in the emergency department, death was found to be 7.7-times more common among those whose treatment didn't follow the TEG-guided treatment algorithm (17 of 28 [60.7%] compared to four of 72 [5.6%], $p < 0.0001$). Other outcomes were also poorer in such patients compared to those whose care followed the algorithm, reported researchers in *Critical Care Explorations*… (*Medpage Today*)

RAS Inhibitors in Hospitalized COVID-19 Patients: REPLACE COVID Trial Findings

Hospitalized COVID-19 patients may safely continue taking ACE inhibitors and ARBs, suggests the REPLACE COVID trial.

The study's primary hierarchical endpoint - a global rank score in which patients were ranked by the severity of COVID disease course based on various biomarkers and clinical events, with a lower rank score suggesting more severe COVID-19 hospitalization - was about the same, whether patients were randomized to continue or discontinue these blood pressure drugs (median rank 73 vs. 81, β-coefficient 8, 95% confidence interval [CI] –13 to 29). Continuation and discontinuation arms also exhibited no differences in the secondary endpoints of all-cause death (15% vs. 13% [$p = 0.99$]); at least one adverse event (39% vs. 36% [$p = 0.77$]); length of hospitalization (6 vs. 5 days [$p = 0.56$]). The findings are published online in *The Lancet Respiratory Medicine*… (*Medpage Today*)

Dupilumab Controlled Itch Intensity, Frequency in Children with Severe Eczema

Treatment with dupilumab with concomitant topical corticosteroids led to rapid and sustained improvement in itch intensity and frequency in children 6-11 years of age with severe atopic dermatitis, revealed a post hoc analysis of a phase 3 trial LIBERTY AD PEDS (NCT03345914), presented at the Revolutionizing Atopic Dermatitis virtual symposium.

On the Peak Pruritus Numerical Rating Scale (NRS), treatment with dupilumab was found to be associated

with a significant improvement from baseline in daily worst itch score through Day 22 in the 300-mg q4w group and the 200-mg q2w group, compared with placebo (–29% vs. –30%, respectively; $p \leq 0.001$ and $p \leq 0.05$). Dupilumab treatment was also associated with a significant improvement from baseline in weekly average of daily worst itch score through Week 16, compared with placebo (–55% vs. –58%; $p \leq 0.001$). A higher daily proportion of dupilumab-treated patients attained a 2-point or more improvement in worst itch score, compared with placebo (51% vs. 49%; $p \leq 0.001$ and $p \leq 0.05$). The same association was noted for the daily proportion of dupilumab-treated patients attaining a 4-point or more improvement in worst itch score, compared with placebo (21% in both groups; $p \leq 0.05$)… (*Medscape*)

UNICEF, WHO, IFRC, MSF Announce Establishment of Global Ebola Vaccine Stockpile

Four leading international health and humanitarian organizations have announced the establishment of a global Ebola vaccine stockpile in a bid to ensure outbreak response.

The effort was led by the International Coordinating Group (ICG) on Vaccine Provision, which includes the World Health Organization (WHO), UNICEF, the International Federation of Red Cross and Red Crescent Societies (IFRC), and Médecins Sans Frontières (MSF). The financial support is provided by Gavi, the Vaccine Alliance. The stockpile will help countries to control future epidemics of Ebola by ensuring timely access to vaccines for populations at risk. The Ebola vaccine was licensed by the European Medicines Agency in November 2019, and is prequalified by WHO. It is licensed by the US Food and Drug Administration (FDA) as well as in 8 countries in Africa… (*WHO*)

Brown Fat Linked with Lower Rates of Cardiometabolic Disease

People with brown fat detected on imaging appear to be at reduced risk of cardiac and metabolic conditions, ranging from type 2 diabetes to hypertension and coronary artery disease, and the effect is particularly strong in individuals with obesity, suggests a new study conducted in over 52,000 individuals who had PET/CT scans as part of cancer evaluation.

The new study, which is the largest of its kind in humans, confirms the health benefits of brown fat that have been proposed by previous studies. Brown adipose tissue was found in 9.7% of patients, with higher rates of brown fat noted among women compared to men (13.8% vs. 4.9%; $p < 0.0001$) and reduced rates with advancing age. Among those with brown fat, the rate of type 2 diabetes was 4.6% compared to 9.5% in those with no brown fat ($p < 0.0001$). A multivariate analysis revealed that the odds ratio (OR) for type 2 diabetes in the presence of brown fat was 0.44. The occurrence of coronary artery disease was also significantly lower in those with brown fat (OR, 0.68; $p = 0.0002$), as was cerebrovascular disease (OR, 0.77; $p = 0.0317$), congestive heart failure (OR, 0.62; $p = 0.0043$) and hypertension (OR, 0.85; $p = 0.0014$). The findings are published online in *Nature Medicine*… (*Medscape*)

Vitamins C and E Tied to Reduced Risk for Parkinson's Disease

Higher intake of vitamins C and E was found to be linked with a decreased risk for Parkinson's disease (PD) in an analysis of a national cohort study.

Higher intake of both the vitamins, in contrast to one, strengthened the association with reduced PD risk. Furthermore, body mass index (BMI) and coffee consumption appeared to affect the magnitude of the effect of these vitamins on PD risk. Dietary beta-carotene and dietary nonenzymatic antioxidant capacity (NEAC) were found to have no impact on this risk. According to EssiHantikainen, PhD, a postdoctoral researcher at the University of Milano-Bicocca, Milan, Italy, the study suggests that the protective effect of dietary vitamins on PD risk might be restricted to specific vitamins, such as vitamin E and C. The findings were published online in *Neurology*… (*Medscape*)

Greater Reductions in Knee OA Pain with Supportive Shoes vs. Flexible Ones

Patients with knee osteoarthritis (OA) who wear stable supportive shoes for 6 months seem to have greater average reductions in knee pain when walking, in comparison with patients who wear flat flexible shoes, suggested a randomized trial of over 160 patients.

The primary outcomes included changes in walking pain on a 0-10 scale and physical function evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index subscale at 6 months. In the flat flexible shoe group, overall average knee pain while walking was found to decline from 6.3 at baseline to 5.2 at 6 months while in the stable supportive shoe group, knee pain while walking decreased from 6.1 to 4. The between-group difference in change in pain was in favor of stable supportive shoes, with a mean difference of 1.1 units. Improvements in knee-related quality of life and ipsilateral hip pain also favored stable supportive

shoes. The findings are published in *Annals of Internal Medicine*… (*Medscape*)

Smoking Heightens Risk of Colorectal Neoplasia in IBD Patients

Active and passive cigarette smoke exposure was found to raise the risk of colorectal neoplasia in patients with inflammatory bowel disease (IBD), suggested a cohort study from the Netherlands. Incorporating this risk factor would improve current risk stratification for surveillance strategies for colorectal neoplasia.

Researchers noted that by IBD type, past smoking heightened the risk for colorectal neoplasia in ulcerative colitis (UC), with a hazard ratio (HR) of 1.73 (95% CI 1.05-2.85), while passive smoke exposure had no impact. For those with Crohn's disease (CD), both active and passive smoke exposure significantly increased the risk, with HR of 2.20 (95% CI 1.02-4.76) and 1.87 (1.09-3.20), respectively. The study is published online in *Clinical Gastroenterology and Hepatology*… (*Medpage Today*)

Dr. Reddy's Receives Approval for Phase 3 Clinical Trial for Sputnik V in India

Dr. Reddy's Laboratories Ltd has announced that the Drugs Controller General of India (DCGI) has given the company approval to carry out the phase 3 clinical trial for the Sputnik V vaccine in India.

The trial will be conducted on 1,500 individuals as part of the randomized, double-blind, parallel-group, placebo-controlled study in the country. The Data and Safety Monitoring Board (DSMB) had earlier reviewed the safety data from the phase 2 clinical trial of the vaccine and had recommended phase 3 recruitment. The DSMB had concluded in its report that there were no safety concerns and the study met the primary endpoints of safety… (*ET Healthworld*)

Asthma-COPD Overlap: High Disease Burden

Patients with asthma-chronic obstructive pulmonary disease overlap (ACO) were found to experience a higher burden of disease, compared to patients with either asthma or COPD alone, reported a new study published in *Respirology*.

In the cross-sectional, observational study, patients aged 18 years and older with a confirmed diagnosis of COPD only (153), severe asthma only (64) or ACO (106), were enrolled. Eosinophilic airway disease was observed in 41% of the patients - 55%, 44% and 29% for those with ACO, severe asthma and COPD, respectively. It was noted that patients with eosinophilic ACO had significantly more past-year exacerbations, particularly those that needed oral corticosteroids, compared with patients with asthma alone… (*Medscape*)

CDC: New, Contagious Coronavirus Variant could Worsen Pandemic

New, more contagious variants of coronavirus are likely to accelerate the spread of the virus, and the US should double down on efforts to protect people, stated the US Centers for Disease Control and Prevention (CDC).

B.1.1.7, the variant first detected in Britain, is being found in the US as well, and modeling suggests that it could worsen the spread of the virus across the country, noted the CDC researchers. This emphasizes that people must try harder to wear masks, avoid gatherings and practice social distancing. Dr. Gregory Armstrong and colleagues wrote in the CDC's weekly report, the MMWR, that evidence suggests that B.1.1.7 is more efficiently transmitted in comparison with other severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants… (*CNN*)

Childhood Insulin Levels Linked with Later Psychosis

A new study has shown a link between elevated insulin levels in childhood and psychosis in young adulthood. The analysis also showed an association between high childhood BMI and depression.

The study, published online January 13 in *JAMA Psychiatry*, suggests that there might be a cardiometabolic signature that predates psychiatric problems that appear in patients during mid-20s. Investigators noted that the persistently high fasting insulin level trajectory was linked with the psychosis at-risk mental state (adjusted odds ratio [aOR] 5.01; 95% CI, 1.76-13.19) and psychotic disorder (aOR, 3.22; 95% CI, 1.11-9.90) at 24 years of age. This trajectory was not associated with depression. For BMI, the puberty-onset major increase trajectory was tied to a higher risk for a depressive episode (aOR, 4.46; 95% CI, 2.38-9.87) at age 24 years… (*Medscape*)

More Transmissible Coronavirus Variant could Dominate by March, Cautions CDC

Just over a month since investigators from the UK warned about the emergence of a new, more transmissible SARS-CoV-2 variant, CDC investigators have cautioned that this new variant will predominate across the United States by the month of March.

As of January 13, the B.1.1.7 variant of SARS-CoV-2 was identified in 76 cases across 10 states in the US, reported researchers in an early release of the CDC's *Morbidity*

and Mortality Weekly Report (MMWR). Modeling predicts rapid growth of the variant in early 2021.

CDC researchers have stressed on the measures to control the pandemic, especially considering the B.1.1.7 variant, including wearing masks, practicing social distancing, hand hygiene, isolation and quarantine measures… (*Medscape*)

COVID-19 Vaccine for Multiple Sclerosis Patients?

The National Multiple Sclerosis Society has advised that most people with relapsing and progressive forms of multiple sclerosis (MS) should get a COVID-19 vaccine.

The new guidance is similar to those issued by the MS International Federation and other organizations and refers to mRNA vaccines by Pfizer/BioNTech and Moderna only. The risks of COVID-19 disease outweigh the potential risks from the vaccine, stated National MS Society experts. They added that members of the same household and close contacts must also receive a COVID-19 vaccine when available to diminish the impact of the virus. They stated that on the basis of data from previous studies of other vaccines and disease modifying therapies (DMTs), getting the COVID-19 vaccine while on any DMT appears safe… (*Medpage Today*)

One Alcoholic Drink a Day Tied to Risk of Atrial Fibrillation

People who regularly consume a modest amount of alcohol have a heightened risk of atrial fibrillation, suggests a study of around 1,08,000 individuals.

Investigators noted that in comparison with drinking no alcohol at all, just one alcoholic drink per day was associated with a 16% increased risk of atrial fibrillation over an average (median) follow-up of around 14 years.

It was also noted that while low doses of alcohol had a link with a reduced risk of heart failure compared to those who never drank alcohol, a similar 'J' shape reduction in risk was not evident for atrial fibrillation, thus suggesting that the elevated risk of atrial fibrillation among those drinking small amounts of alcohol was not caused by heart failure. The findings are published in the *European Heart Journal*… (*HT – ANI*)

GACVS COVID-19 Vaccine Safety Subcommittee Meets to Review Death Reports of Frail Elderly Vaccinated with Pfizer-BioNTech Vaccine

The GACVS COVID-19 Vaccine Safety subcommittee convened virtually on January 19, 2021 to review the data on deaths that have been reported among frail, elderly individuals who were administered the Pfizer-BioNTech COVID-19 mRNA vaccine, BNT162b2.

On the basis of scientific review of the information available, the subcommittee concluded that the reports do not indicate any unexpected rise in deaths in frail, elderly individuals. Additionally, there is no indication of any unusual characteristics of adverse events after vaccine administration.

The reports are in agreement with the expected all-cause mortality rates and causes of death in the frail, elderly sub-population. The information that is available does not suggest that the vaccine contributed to the reported fatalities. The committee thus considered that the benefit-risk balance of the vaccine was favorable in the elderly, and did not suggest any revision to the recommendations around its safety… (*WHO*)

Metabolic Surgery Effective as Long-term Diabetes Cure

A randomized trial of 60 patients with type 2 diabetes and obesity, published in the *Lancet*, revealed that diabetes remission rates were found to be significantly higher in the years following surgery, in comparison with conventional medical therapy.

The 2-year outcomes reported earlier had suggested that diabetes remission was attained in 75% of patients who underwent Roux-en-Y gastric bypass (RYGB) and 95% of patients who underwent biliopancreatic diversion (BPD). Diabetes remission was characterized by an HbA1c below 6.5% and fasting glucose <100 mg/dL (5.55 mmol/L) in the absence of ongoing pharmacological treatment for at least a year.

The 10-year outcomes revealed that 50% of the patients who underwent BPD could maintain diabetes remission by year 10. Additionally, 25% of those who underwent RYGB could maintain their remission at 10 years… (*Medpage Today*)

Australia Approves Pfizer COVID-19 Vaccine

Australia granted approval to the Pfizer-BioNTech COVID-19 vaccine for use on January 25, 2021; however, it cautioned that issues with AstraZeneca's international production suggest that the country would have to roll out a locally manufactured vaccine earlier than planned.

Vaccination with the Pfizer vaccine for the priority groups is expected to start in late February, at an estimated rate of 80,000 doses per week, stated Health Minister Greg Hunt. Australia will begin CSL's domestic supply of the AstraZeneca vaccine in March, which is earlier than planned, at a rate of 1 million doses per

week. Australia has a target of 4 million doses of vaccine by April… (*Reuters*)

CDC Reviewing New Data that Suggests UK Coronavirus Variant could be More Fatal Immune System of Recovered COVID-19 Patients may Even Fight Variants

Individuals who recover from COVID-19 are protected against the virus for at least 6 months, probably much longer, suggests a new study published in the journal *Nature*. The study further indicates that the immune system continues to evolve long after the infection and may block even the virus variants such as the South African variant.

Investigators observed that antibodies produced by immune cells keep evolving, which could likely be due to sustained exposure to remnants of the virus in the gut tissue. The scientists state that this study has provided the strongest evidence so far that the immune system remembers the virus and continues to improve the quality of antibodies even after the infection dwindles… (*HT – PTI*)

Full-dose Clot Prophylaxis Beneficial in Moderate COVID-19

Findings from three large platform trials suggest that therapeutic anticoagulation for thromboembolic prophylaxis was associated with improved outcomes and possibly survival in hospitalized but not critically ill COVID-19 population.

The full-dose treatment approach was found to be superior to prophylactic dosing for decreasing the proportion of patients progressing to ventilation requirement and other vital organ support across the three adaptive platform trials ACTIV-4a trial, REMAP-CAP and ATTACC. Therapeutic dosing appeared to be safe in the moderately ill COVID-19 patients, contrary to the critically ill population, for which the trials had to stop the full-dose strategy after indications of harm. Complete results of the three trials will be released later… (*Medpage Today*)

Patients with Inactive Cancer Face High Risk of Severe COVID-19 Disease

A new study, published in the journal *JNCI Cancer Spectrum*, has revealed that patients with inactive cancer who are not undergoing treatments at present also have a significantly higher risk of severe illness from COVID-19.

Investigators assessed the records of over 4,800 patients tested for COVID-19 from the Penn Medicine BioBank and evaluated the association between cancer status and COVID-19 outcomes. Among the 328 cases that were positive through June 2020, the medical history of 67 (20.7%) of them had a cancer diagnosis, with 80.6% having solid tumor malignancy and 73.1% having inactive cancer. Patients with COVID-19, both with active cancer and inactive cancer, were found to have higher rates of hospitalizations in comparison with patients who did not have cancer (55.2% vs. 29%), admission to intensive care unit (25.7% vs. 11.7%), and 30-day mortality (13.4% vs. 1.6%)… (*HT – ANI*)

Israel Starts Vaccinating 16- to 18-year Olds Ahead of Exams

Israel has started inoculating 16- to 18-year olds against COVID-19. The measure comes as an effort to allow them to appear for the approaching examinations.

Over a quarter of Israel's population of 9 million people have been given at least one dose of the Pfizer vaccine since December 19, 2020, stated its health ministry. The vaccination was started with the elderly and those at high risk. Now, individuals aged 40 and over can also get the shot. The country expects to start reopening its economy in February. An education ministry spokeswoman stated that the inclusion of 16- to 18-year olds, with parental permission, is intended at enabling their return to school and to hold the exams in an orderly fashion… (*BBC*)

Low-dose IL-2 Promising in Colitis

According to findings from an 8-week study presented at the virtual Crohn's and Colitis Congress, low doses of the recombinant T-cell growth factor interleukin 2 (IL-2) were tolerated well by patients with moderate-to-severe UC. Only one patient withdrew owing to a dose-limiting toxicity, reported an investigator.

About 38.4% of the patients enrolled in the study achieved a clinical response and 15.4% were in clinical remission by Week 8, reported Jessica R Allegretti, MD, of Harvard University in Boston. Low-dose subcutaneous IL-2 was found to be well-tolerated and yielded a biological response and peripheral Treg expansion among moderate-to-severe UC patients. The maximum effective dose was 1×10^6 IU/m^2/day… (*Medpage Today*)

WHO Recommends Dapivirine Vaginal Ring for HIV Prevention Among Women at Considerable Risk

The WHO has recommended the use of dapivirine vaginal ring (DPV-VR) as an added option for women

at considerable risk of human immunodeficiency virus (HIV) infection. DPV-VR has to be used as a component of combination approaches for the prevention of HIV infection.

It was noted in two Phase III randomized controlled trials that the use of DPV-VR diminished the risk of HIV infection among women and long-term use of the treatment approach was well-tolerated. In the Ring Study, there was an HIV risk reduction of 35% for women who used DPV-VR, while the ASPIRE study demonstrated a risk reduction of 27%.

The ring has to be worn inside the vagina for 28 days, following which it has to be replaced with a new ring. This silicone ring can be easily bent and inserted. It releases the drug dapivirine into the vagina gradually over a period of 28 days… (*WHO*)

With Right Precautions, In-person Learning Possible During Pandemic: CDC

Researchers from the US CDC have suggested that if appropriate measures to check the spread of coronavirus are followed, low-risk, in-person learning is possible.

According to a paper appearing in the *Journal of the American Medical Association*, researchers suggest that the type of COVID-19 transmission that has been noted in crowded offices and long-term care facilities has not been observed in schools. Though transmission has been reported in schools, it does not appear to have led to enhanced community transmission. Two studies from the CDC, published in *Morbidity and Mortality Weekly Report*, also suggest that amid adequate precautions, children can safely go to school… (*CNN*)

Colchicine for Early COVID-19

Findings from the COLCORONA trial suggest that the anti-inflammatory drug colchicine improved COVID-19 outcomes among patients with relatively mild disease.

The drug was found to diminish the risk of death or hospitalizations by 21% in comparison with placebo. The results reached statistical significance. A significant effect was evident in the 4,159 patients out of 4,488 with COVID-19 confirmed by a positive polymerase chain reaction (PCR) test. There were 25% fewer hospitalizations, 50% less requirement of mechanical ventilation, and 44% fewer deaths. According to principal investigator Jean-Claude Tardif, the findings point to the efficacy of treatment with colchicine in preventing cytokine storm and decreasing the complications tied to COVID-19… (*Medpage Today*)

Updated Definitions of Extensively Drug-resistant Tuberculosis Announced by WHO

The World Health Organization (WHO)'s Global TB Programme has revised the definition of extensively drug-resistant tuberculosis (XDR-TB). Pre-XDR-TB has also been defined for the first time. The move emphasizes the significance of these forms of tuberculosis (TB).

New definitions for these forms of TB will assist with the precise characterization of different groups of patients with TB in need of complex treatment regimens. They may also help with improved reporting, surveillance as well as monitoring of drug-resistant TB in countries across the world. The new definitions are also expected to encourage the development of better treatment approaches for these dangerous forms of TB… (*WHO*)

Schizophrenia Associated with Higher Risk of COVID-19 Mortality

Individuals with schizophrenia appear to have a higher risk for severe COVID-19, suggests a new study published in *JAMA Psychiatry*.

Katlyn Nemani, MD, of New York University Langone Medical Center in New York, and associates noted that in comparison with COVID-19 patients without a psychiatric disorder, those with schizophrenia spectrum disorder appeared to have a more than two-fold higher risk for mortality within 45 days of a confirmed case, with an OR 2.67. Individuals with other mood disorders (OR 1.14, 95% CI 0.87-1.49) or anxiety disorders (OR 0.96, 95% CI 0.65-1.41) were not found to have an increased risk of COVID-related death… (*Medpage Today*)

Over a Third of COVID-19 Infections Asymptomatic, Says Review

A systematic review, published online in *Annals of Internal Medicine*, suggests that at least one third of SARS-CoV-2 infections remain asymptomatic. The review provides robust evidence for the prevalence of asymptomatic infections.

Investigators stated that the finding that about one in three people infected with COVID-19 do not develop any symptoms is an indication that testing needs to be changed. Lead author Daniel Oran stated that in order to limit the transmission of the virus from presymptomatic or asymptomatic individuals, the testing focus needs to be shifted to at-home screening.

The highest-quality evidence in this systematic review comes from large studies in England and Spain. The proportion of asymptomatic cases was 32.4% in England while it was 33% in Spain… (*Medscape*)

WHO Launches 10-year Plan to Tackle Neglected Tropical Diseases

The WHO has issued a new road map for neglected tropical diseases (NTDs) that puts forward targets as well as innovative approaches to handle 20 diseases known to affect over a billion people, particularly the poor. The diseases are common in areas where there is insufficient access to quality health services, clean water and sanitation.

"*Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021-2030*" proposes key 2030 global targets, including 90% reduction in the number of people that need treatment for NTDs; elimination of at least one NTD in at least 100 countries; eradication of two diseases - dracunculiasis and yaws; and 75% reduction in the disability-adjusted life years (DALYs) related to NTD… (*WHO*)

People on Blood Thinners can Receive Vaccine: ICMR

Fact-sheets of Covaxin and Covishield are soon going to be revised to allow individuals on blood thinners such as aspirin and clopidogrel to receive the vaccines. People taking anticoagulants may also take the vaccine with certain precautions, says the Indian Council of Medical Research Director General Dr Balram Bhargava. At present, the fact-sheets of the vaccines state the use of blood thinners as a contraindication. Additionally, Dr Bhargava stated that Covaxin's response to the UK strain appears to be as effective as that against the virus seen in India. People on blood thinners may experience a swelling at the injection site. Dr Bhargava added that antiplatelet agents like aspirin or clopidogrel do not pose a problem. However, for those taking anticoagulants like heparin, there may be a tendency to bleed. There may be a risk of a local hematoma, which is a relative contraindication… (*ET Healthworld – TNN*)

One in 3 Adults Suffer Psychological Distress Due to COVID-19

One in every 3 adults, particularly younger adults, women, and those belonging to the lower socioeconomic status, suffer psychological distress related to COVID-19, suggests a new study published in *PLOS ONE*.

Investigators conducted a meta-analysis of 68 studies that were carried out during the pandemic, and included 2,88,830 participants across 19 countries. They evaluated the risk factors associated with anxiety and depression among the general population. It was noted that for people most affected by COVID-19-related anxiety or depression, women, younger adults, those of lower socioeconomic status, those living in rural areas, and those having a high risk of COVID-19 infection had increased likelihood of experiencing psychological distress… (*HT – ANI*)

WHO Publishes New Essential Diagnostics List

The WHO, since 2018, has been publishing an essential diagnostics list (EDL) every year in order to address inadequate access to tests and testing services in several countries. The list includes the recommended *in vitro* diagnostics that must be available at point-of-care and in laboratories across all countries to assist with timely diagnoses.

The agency has published the latest edition of the list which includes WHO-recommended COVID-19 tests, both PCR and antigen tests. It also expands the series of tests for vaccine-preventable, infectious as well as noncommunicable diseases, and also introduces a section on endocrinology. The list, for the first time, includes tests that should not be supplied in countries, either on account of their poor cost-effectiveness, unreliability or having been overtaken by newer, easier to use tests… (*WHO*)

Full-dose Heparin Beneficial for Moderate COVID-19 Irrespective of D-dimer

Interim pooled findings from the ACTIV-4a, ATTACC, and REMAP-CAP trials suggest that full-dose prophylactic anticoagulation is considerably beneficial for moderately ill COVID-19 patients irrespective of the initial D-dimer level.

For the primary endpoint, organ support-free days to Day 21, in hospitalized patients initially not in the intensive care unit (ICU), the therapeutic dose approach had a proportional odds ratio meeting the criteria for superiority over typical prophylactic dose - 1.57 with low D-dimer, 1.53 with high D-dimer and 1.51 with missing D-dimer. Overall, the rates were around 16% vs. 23% in post hoc analysis, reported Ryan Zarychanski, leading both ATTACC and REMAP-CAP trials… (*Medpage Today*)

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Importance of Silence

KK AGGARWAL

In a US-based study, dying people were asked about their regrets, if any. The top five regrets were:

1. I wish I had the courage to live a life I wanted to live and not what others expected me to live.
2. I wish I had worked harder.
3. I wish I had the courage to express my feelings.
4. I wish I had stayed in touch with my friends.
5. I wish I had let myself to be happier.

Regrets are always based on suppression of emotions or nonfulfilment of desires and needs. These need-based desires can be at the level of physical body, mind, intellect, ego or the soul. Therefore, regrets can be at any of these levels.

I did a survey of 15 of my patients and asked them a simple question that if they come to know that they are going to die in next 24 hours, what would be their biggest regret. Only one of them, a doctor, said that she would have no regrets.

Only one person expressed a physical regret and that was from a Yoga expert who said that her regret was not getting married till that day.

Mental regrets were two:

1. A state trading businessman said, "I wish I could have taken care of my parents."
2. A Homoeopathic doctor said, "I wish I could have given more time to my family."

Intellectual regrets were three:

1. A lawyer said, "I wish I could have become something in life."
2. A businessman said, "I wish I could have helped more people."
3. A retired revenue inspector said, "I wish I had married off my younger child."

Egoistic regrets were two:

1. One fashion designer said, "I wish I could have become a singer."
2. A housewife said, "I wish I could have become a dietician."

Spiritual regrets were six:

1. A Consultant Government Liaison officer said, "I wish I could have made my family members happy."
2. A businessman said, "I wish I could have meditated more."
3. A Homoeopathic doctor said, "I wish I could have spent more time with my family."
4. A reception executive said, "I wish I could have spent more time with my parents."
5. An entertainment CEO said, "I wish I could have taken my parents for a pilgrimage."
6. A fashion designer said, "I wish I could have worked more for the animals."

In a very popular and successful movie, Kal Ho Na Ho, the hero was to die in the next 40 days. When asked to remember the days of his life, he could not remember 20 ecstatic instances in life.

This is what happens with each one of us where we waste all our days and cannot remember more than 50 or even 20 of such instances. If we are given 40 days to live and if we live every day ecstatically, we can get inner happiness. Therefore, we should learn to live in the present instead of having a habit of postponing everything we do.

We should learn to prioritize our work and do difficult work first or else we would be in a state of constant worry till that work is over.

I teach my patients that they should practice confession exercise and one confession is to talk about your regrets and take them as challenge and finish. When working, there are three things which are to be remembered – passion, profession and fashion. Profession is at the level of mind, ego and spirit.

We should convert our profession in such a manner that it is fashionable and passionate. Passion means working from the heart and profession means working from mind and intellect and fashion means working the same at the level of ego which is based on show-off.

Group Editor-in-Chief, IJCP Group

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The Mango Tree

Once upon a time, there lived a big mango tree. A little boy loved to come and play around it every day. He climbed to the tree top, ate the mangoes and took a nap under the shadow… He loved the tree and the tree loved to play with him.

Time went by… The little boy grew, and he no longer played around the tree. One day, the boy came back to the tree with a sad look on his face. "Come and play with me," the tree asked the boy.

"I am no longer a kid, I don't play around trees anymore." The boy replied, "I want toys. I need money to buy them." "Sorry, I don't have money… but you can pick all my mangoes and sell them so you will have money."

The boy was so excited. He picked all the mangoes on the tree and left happily. The boy didn't come back. The tree was sad. One day, the boy, grown into a man, returned. The tree was so excited. "Come and play with me," the tree said.

"I don't have time to play. I have to work for my family. We need a house for shelter. Can you help me?" "Sorry, I don't have a house, but you can chop off my branches to build your house." So, the man cut all the branches off the tree and left happily. The tree was glad to see him happy but the boy didn't come back afterward. The tree was again lonely and sad.

One hot summer day, the man returned and the tree was delighted. "Come and play with me!" The tree said. "I am sad and getting old. I want to go sailing to relax myself. Can you give me a boat?" "Use my trunk to build your boat. You can sail far away and be happy."

So, the man cut the tree trunk to make a boat. He went sailing and didn't come back for a long time. Finally, the man returned after he had been gone for so many years. "Sorry, my boy, but I don't have anything for you anymore. No more mangoes to give you." The tree said.

"I don't have teeth to bite," the man replied. "No more trunk for you to climb on." "I am too old for that now," the man said. "I really can't give you anything… the only thing left is my dying roots," the tree said with sadness. "I don't need much now, just a place to rest. I am tired after all these years," the man replied. "Good! Old tree roots are the best place to lean on and rest. Come sit down with me and rest."

The man sat down and the tree was glad and smiled.

Moral: The tree in the story represents our parents. When we are young, we love to play with them. When we grow up, we leave them and only come back when we need help. Parents sacrifice their lives for us.

■■■■

Do Babies Get Enough Protection from Mother's COVID Antibodies?

New research suggests that mothers with COVID-19 produced a strong antibody response; however, the antibody transfer across the placenta to the infants was less efficient than what was anticipated.

A study conducted among pregnant women who had COVID-19 infection detected neutralizing activity in 94% of maternal blood samples but only 25% of cord blood samples, reported researchers. The overall cord-to-maternal anti-receptor binding (RBD) immunoglobulin (Ig)G ratio was found to be 81%. The findings were presented at the annual meeting of the Society for Maternal-Fetal Medicine. Naima Joseph, of Emory University in Atlanta, stated during her presentation that though anti-RBD domain IgG titers were identified in umbilical cord samples, the efficiency of transfer was found to be less than 1… (*Medpage Today*)

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Lighter Side of Medicine

HUMOR

NO + NO = YES

In a mathematics class the teacher told the student that minus * (times) minus –*– = + and also NO + NO = Yes. So, a boy was pressed to go to toilet. He then asked the teacher, "Excuse me, sir, can I use the toilet?" The teacher said, "No." The student asked again, "Excuse me, sir, can I use the toilet?" The teacher said, "NO."

Immediately student stood up to go to the toilet, the teacher was surprised and said, "Where are you going?" He said, "Toilet." The teacher asked him, "Why?" He said, "NO + NO = Yes, so since you said NO two times I know you mean yes." So, the class burst into laughter.

COMMUNICATION TECHNICIAN

A communication technician drafted by the army was at a firing range. At the range, he was given some instructions, a rifle and 50 rounds. He fired several shots at the target. The report came from the target area that all attempts had completely missed the target. The technician looked at his weapon, and then at the target. He looked at the weapon again, and then at the target again. He then put his finger over the end of the rifle barrel and squeezed the trigger with his other hand. The end of his finger was blown off, whereupon he yelled toward the target area: "It's leaving here just fine, the trouble must be at your end!"

WHAT IT MEANS

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

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

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

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

AN ADDICTION

Connie told her 4-year-old grandson not to jump on the beds. After several warnings she punished him, explaining that should he fall, he would hurt himself badly.

Several minutes passed and he was back to jumping on the beds.

Connie said, "You weren't jumping on the beds again, were you?"

He stood with his little head dropped low and said, "I'm trying, but it's so hard to quit."

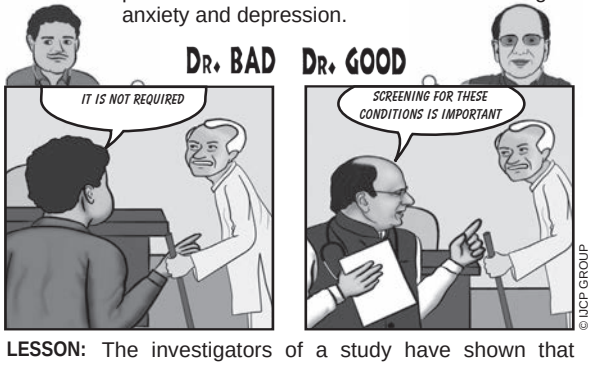
BANK NAME

Mother decided that 10-year-old Cathy should get something 'practical' for her birthday. "Suppose we open a savings account for you?" mother suggested. Cathy was delighted. "It's your account, darling," mother said as they arrived at the bank, "so you fill out the application."

Cathy was doing fine until she came to the space for 'Name of your former bank.' After a slight hesitation, she put down 'Piggy.'

Dr. Good and Dr. Bad

SITUATION: A 71-year-old man with type 2 diabetes and nephropathy admitted to the hospital since the past 2 weeks was recommended screening for anxiety and depression.



LESSON: The investigators of a study have shown that a large proportion of hospitalized patients with diabetes develop moderate/severe anxiety or depression or both during hospitalization. Thus, screening for these conditions in high-risk hospitalized diabetic patients is advised. According to this study, physical inactivity and staying for ≥8 days in the hospital were associated with the risk of anxiety while older age, low income and nephropathy were related to depression.

Med Princ Pract. 2017;26:548-53.

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

Books

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

Articles in Books

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