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Editorial

Rural Obstetrics — A Realistic problem in India

Dr Samarendra Kumar Basu
MBBS, DGO, FIMAMS (GO) FELLOW (IAOG),
Consultant, Senior Gynaecologist and Obstetrician,
Trained in Infertility Management, Laparoscopist
Hony Editor, Journal of IMA (JIMA)

In India, a vast population resides at rural areas. The Irony of the fact that in spite of all useful efforts taken from the department of health and welfare, obstetrical care is still done by unskilled persons in the majority till date.

Government of India accepted the programme " Health for all by 200 AD". Unfortunately this programme is still remain in paper with rural obstetrics remaining unchanged.

Percentage of rural obstetrics in India — 80% of all obstetrics done in our country is rural obstetrics .Accordingly 25 millions pregnant women need care for safe mother hood and 20 millions deliveries to be conducted in a year - very hard and enormous job.

In a developing country like us, an women is at risk of three hundred times more of morbidity and mortality in pregnancy and child birth compared to an women in developed country. Number of women die in a year in America is equal to number of women die in India in a week. Thus rural obstetrics is a genuine chapter to look nearly and sincerely in near future.

Maternal Mortality & morbidity in rural Obstetrics :-

Recent modernization of medical science and advent of higher antibiotics is now in our hand. Though the maternal, Mortality & Morbidity in rural obstetrics is alarming. In 1998 the mortality rate is 407 per and morbidity is 2060 per 1 lac deli varies. If we sub divide the reasons it will be as follows:-

(1) Due to Sepsis – 28%, (2) Due to Haemorrhage – 24%,
(3) Hypertension – 20%, (4)Medical disorder in pregnancy- 11%,
(5)Anasthetic & Operative complication- 17%.

Factor responsible for these complications in rural obstetrics —

(1) Illiteracy
(2) Social & Religious Stigma
(3) Non availability and non utilization of Scientific facilities available
(4) Lack of proper motivation
(5) Lack of proper transport facility and communication gap.
(6) Lack of proper hygiene and nutrition

An interesting study was conducted in 2012 KEM Hospital, Pune which says that

- 24% expectant mother who needed to be refer in a better hospital, died at home
- 19% expectant mother died on their way to hospital.
- 10% expectant mother died due to lack of proper facility or due to improper handling by untrained Quacks & Dhais.
- 47% arrived at right obstetrical centre out of those 42% were late to come at this centre and died within 12 hrs of admission.

These above picture definitely forced us to look and to evaluate the proper preventive and curative measures to arrest the unwanted health hazards in rural obstetrics.

Despite a 5 (five) decade old Family Welfare Program India still continue to contribute a quarter of the Global Estimates maternal Morbidity & Mortality. Quality Maternal Health Care have long been ignored in the Indian Public Health System. Thus the launch of the National Rural Health Mission (NRHM) that quality care has been accorded due to recognition in the National Health Progamme.

This programme aims to examine the scenario, the quality of care in maternal health over the last decade and scope for further improvements. WHO estimates indicate that out of 530000 Maternal death globally in each year, 117000 (22%) occur in India.

In addition to these millions suffer pregnancy related morbidity and contribute 21% of the disability adjusted life year lost due to the maternal condition. Public health initiative over the last 2-3 decades have helped India to improve this condition.

On the contrary after such policies still crucial indications like Maternal Mortality Rate (MMR) and Infant Mortality Rate (IMR) have stagnated at around 400 per 100000 live births and 60 per thousand live births respectively.

The National Rural Mission which was launched in April, 2005 " To provide accessible, affordable, and quality health care to the rural sections especially in vurnerable Population". This ambition goes .to reduce the (MMR), from existing ratio to 100 per 10000 ratio life birth.

The national Family Health Survey-3 (NFHS)-3 conducted in 2005 -3 represented that only 62.4% for every married women respondents living in urban areas who are receiving antenatal care as per (WHO) recommendation compared to 27.7% of rural women. This picture will have to change at least 60% of rural population should get obstetrical care as per WHO recommendation.

Future ways to improve rural obstetrics : —

(1) Centre with proper well equipped facility and facility of minimum caesarean section delivery and blood transfusion facility to be available in every sub-division zone, preferably in primary health care system. This is the main slogan of RCH II programme at present.

(2) Basic Investigation Facilities to be available at rural based level.

(3) Proper transportation facility to shift the expectant mother from a lower centre to a higher centre.

(4) Basic education & health knowledge to every carrying mother.

(5) Trained dhais, Quacks, health Assistant. Untrained persons should be identified and their proper trainings to be arranged.

(6) Every dhais, Quacks, etc should have DHAI KIT having basic materials for home delivery as we cannot ignore home delivery in our present scenario. They should have proper knowledge to identify the high risk cases and should know which cases they should deal and which cases they should refer to higher centre.

(7) Regular antenatal care at primary level preferably at home with availability of basic medicines for pregnant women at their door step.

(8) Adequate family planning advices.

(9) Adequate knowledge regarding age of marriage, proper spacing proper nutrition & hygiene.

(10) Awareness programs at regular basis in rural areas involving political, Social and educated persons of the zone. Here of the zone, different club secretaries and teachers can play a vital role.

We must acknowledge that rural obstetrics cannot looked at separate angle at present. It is very much related with the socioeconomic scenario of our state and the country as well. The infrastructure of health system of rural areas is based on the complex of primary & subsidiary health centres. It was expected that by the end of seventh plan period in 1990, rural health centres should have established to cover the entire rural areas. Since deliveries by trained dhais etc. Are crucial in reducing maternal mortality, Government tof India under took a scheme to train total dhais and health workers which involves huge amount of money. But persistent reduction of health budget and want of a realistic health systems are effecting this scenario of rural obstetrics as well.

More birth rate, higher fertility rate, more still birth & neonatal death etc. defiantly ask us to share more responsibility in this spheres. Because the concept of the right of any expected mother to deliver a child to be mentally, physically and emotionally well being cannot be over looked. The concept of obstetrics as a social as well as a biological science impels us to accept more responsibility to protect the basic right of a pregnant women and their outcome of future generation. It is real truth that when a woman moves rightly, the family as well as the country moves rightly.

Thus the rural obstetrics need total involvement of persons at home upto the highly skilled medical personalities. It starts at home and end in an obstetrical centre. New born is like a beautiful rose and its pleasant presence makes us healthy, hearty and cheerful.

Original Article

Assessing the preparedness and strategies in the management of Dengue disaster in the hospitals

Raman Sharma[1], Meenakshi Sharma [2], Ravneet Kaur[3], Jaswinder Kaur[4], Ravinder Yadav[5], Ram Singh[6], Amarjit Singh[7]

Dengue is fast emerging viral pandemic and incidence has increased over 30-fold the last 50 years. Severe manifestations of dengue outbreaks have always created panic and public have always expected urgent action from healthcare organizations. At such times, it becomes essential to have preparedness and flexibility in the administrative structure to manage such crisis as quickly as possible. The present study was conducted with objectives to assess the preparedness and strategies in the management of dengue cases in Hospitals. A total of 1475 suspected patients were admitted and screened in the Emergency OPD for dengue in 4 months and 250 were confirmed positive. A separate area was designated for giving immediate and transitory medical care. 'May I help you' counter was established at emergency entry for information and instructions to people. One doctor and two nurses were attached for the average load of 50 patients each admitted. Social workers were instructed to get to the each patient individually, counsel them and to answer their queries. They also made daily census. A technician was posted specifically for sampling of suspected patients. Around 200 more trolleys were introduced and trolley men were instructed to conduct frequent hospital rounds and get back the trolleys, as soon as the patient is shifted to ward. Central stores and pharmacy were activated to make necessary logistics and drugs available as per load. Blood and blood components were made readily available to those who needed them. Voluntary donors, doctors and staff members were mobilized.

[*J Indian Med Assoc* 2018; **116: 11-4**]

***Key words* : Infrastructure, logistics, management, manpower, medication, strategies.**

Dengue is fast emerging pandemic-prone viral disease. The incidence has increased 30-fold over the last 50 years[1]. Dengue outbreaks, when associated with severe manifestations always create panic and people expect urgent action from government authorities especially the healthcare organizations.

From hospital point of view, a contingency plan dealing with emergency hospitalization of large number of cases needs to be prepared for making the most effective use of hospital and treatment facilities with its limited resources[2]. So, the main focus of this article is to assess the preparedness and strategies in the management of dengue cases in Hospitals.

Department of Hospital Administration, GMCH, Chandigarh 160030
[1]MBBS, MHA, Senior Resident and Corresponding author
[2]MPH, PhD, Scholar, School of Public Health, PGIMER, Chandigarh
[3]MBBS, MD (Transfusion Medicine), Assistant Professor, Department of Transfusion Medicine, GMCH, Chandigarh 160030
[4]Social worker, Department of Hospital Administration, GMCH, Chandigarh 160030
[5]Medical social worker, Department of Medical Records, GMCH, Chandigarh 160030
[6]MBBS, MD (Internal Medicine), Professor, Department of General Medicine, GMCH, Chandigarh 160030
[7]MBBS, MD (Community Medicine), Professor, School of Public health, PGIMER, Chandigarh 160012

Materials and methods

It is a descriptive study conducted in one of the tertiary level multispecialty hospital of North India, catering to population of Punjab, Haryana, HP, J&K, UP along with Chandigarh itself. The hospital is a 700 bedded hospital with an annual OPD of 4.5 lakhs and IPD of about 40,000 and emergency load of 80,000.

This was a short-term study (October-December 2012). Consent was obtained from the authorities. The physical space, entry and exit system, location, registration area, lobby/corridor, waiting area, examination rooms, observational beds, emergency X-ray room and laboratory, treatment rooms, nurse's station, staff rest rooms, stores, police post and public relations office were observed. In addition, the patient/attendant load, patient flow, and medical staff practice were observed.

The Emergency has three entrances manned by security guards. These open into a spacious, well lit lobby. There are separate emergency wards for medicine and surgery (total 34 beds), and 32 observational beds. The radiology department, two operating theatres, a blood bank, an attendant waiting room and laboratory are also attached to the Emergency. There is one overflow ward attached with emergency to cater the load, but there is no separate isola-

tion facility. On an average, 150-200 patients are admitted daily (average occupancy of 200-250%) and almost twice those numbers of attendants accompany them (Table 1). At any one time, there is one consultant, two senior residents, four nursing staff and four supporting staff members present.

In the month of August, 2012 increased number of patients' started pouring in, with the complaints of acute febrile illness, headache, and rash, myalgia, arthralgia, retro-orbital or ocular pain. The patients were screened, investigated and a formal diagnosis of dengue was established. The diagnosis was established using the NS1 and Immunoglobulins investigations methods.

The need to screen all patients with suspected symptoms and to keep them under direct observation, not to be kept in isolation, was established. The flow of patients and their attendants was not systematic and their movement was uncontrolled and there was a sudden rise in the EMOPD occupancy of up to 300%. Two or three or even more attendants usually accompanied one patient. The corridor was overcrowded, leaving little space for movement of patients, nurses and doctors.

The patients were started with symptomatic treatment, while some of the patients required platelets infusion also. It was observed that on an average it took a week (6-7 days) for the fever to get down along with relapse of other problems. As the patient inflow was much more than the exit of patients, shortly afterwards, the occupancy rate touched around 500% and at that time it became very much essential to arrange the facilities at the early possible.

Table 1 — *Hospital statistics from Government Medical College and Hospital (GMCH), Chandigarh*

Variable (Service)	N
Total no. of hospital beds	700
Total no. of doctors in hospital	168
Doctors in EMOPD at one time	2 (12-hourly shift)
Total no. of nurses in hospital	368
Nurses in EMOPD at one time	4 (6-hourly shift, 12-hourly at night)
Total no. of monthly admissions	3637
Average daily admissions	122
Daily census of indoor patients	562
Maximum on any one day	598
Minimum on any one day	504
Average length of stay (days)	9
Bed occupancy ratio (%)	82.0%
Medical emergency (%)	99.1
Average daily OPD	1800
Total monthly emergency OPD	2783 (11.1% of new patients in hospital)
Total monthly deaths	266
Emergency OPD deaths	238

Reference : EMOPD a Monthly Statistical Report (November 2012), MRD, GMCH 32, Chandigarh, India

Table 2 — *The rise in requirement of Blood and Blood components during the dengue*

Month	Voluntary donors	Plateletpheresis procedures	Platelets units issued	Camps organized
July	1077	6	132	7
August	1430	7	201	10
September	1217	46	713	14
October	1508	167	1382	21
November	867	44	411	11
December	1146	8	193	13

Results

A total of 1475 suspected patients were screened for dengue in 4 months. Out of total, 250 were confirmed positive cases of dengue (Fig 1). There was also a continuous rise in the number of suspected and positive dengue cases reporting to the hospital as compared to last three years (Table 2). In the present year (2012) also, the largest proportion of serologically positive cases have been recorded in the months of September to November.

GMCH EMOPD has a core type of design. The following possible changes were made as for the effective management of emergency cases:

(1) Space allocation: The EMOPD has 21 beds (plus another fixed 16 trolleys), with additional 60-70 trolleys, leaving little scope for further expansion.

So, a specific area was designated for giving immediate and transitory medical care to patients, until they can be transferred to a ward, which included:

- Lobby area of the Medicine Emergency (Space I)
- Lobby area of the surgery Emergency (Space II)
- Area in the emergency in front of the Registration counter (Space III)
- Waiting area at the entry emergency (Space IV)

(2) Function: A range of resources and services were needed to deliver good clinical services and this was done without undue disturbance and cost.

Human Resources :

- Initially, two to three attendants used to accompany a patient along with their baggage. This had led to undue space occupancy and overcrowding. 'May I help you' counter was established at the entry of EMOPD to provide information and instructions to people. A systematic

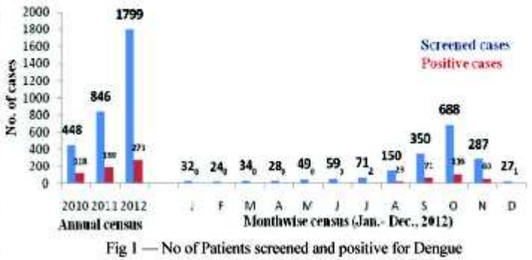

Fig 1 — No of Patients screened and positive for Dengue

patient flow control mechanism was developed and a screening system for patients' attendants was also initiated. Only one attendant (at the most two, in case of serious emergency) was allowed into the EMOPD area. This helped to accommodate more patients in the limited emergency area.

- Patients arriving in EMOPD were first examined thoroughly to rule out the chance of dengue. Doctors were deputed to the first level of care to help in triage and emergency management.

As the patient load was much more, and at one time there used to be 150-200 dengue suspected or diagnosed patients, besides the emergency cases, two doctors and four staff nurses were specifically deputed to manage the dengue cases, while, on routine duty doctors used to manage the emergency services otherwise. One doctor and two nurses were attached for the load of 50 patients each admitted.

One senior most faculty was posted in the Emergency for the overall supervision and management of the emergency functioning.

- As the patient relatives sometimes used to get panicky, stressed and aggressive for their wards, led to undue arguments with doctors and staff on duty, two social workers were specifically deputed to pacify them and answer their queries. Social workers were instructed to get to the each patient individually, develop a repo with them, counsel them, and answer their any query or confusion. They also made daily census with the help of staff nurse on duty and sent the report to authorities.
- Patients/relatives reporting to emergency block for works viz. file clearance, pass issuance etc. were channelized through other routes. Systems were activated to speed up the registration process by inducting more persons, installing more registration counters.

Trolleys :

`The trolleys were one of the important requirements during the management. Earlier, there used to be 150 trolleys in the emergency besides normal beds. But with the surge in the number of cases and on an average 7-10 days stay, it led to the crisis of trolleys in the hospital.

Initially, trolleys were mobilized from the different Hospital wards, but the requirement was not fulfilled. Later, the trolleys from the central store followed by 50 more trolleys were purchased.

Trolley men were told to conduct the hospital rounds more frequently and get the trolleys back to emergency, as soon as the patient is shifted to ward.

Laboratory Facilities:

- Availability of quick and reliable laboratory investigation facilities is vital for the early diagnosis of acute infectious diseases and allows initiation of prompt treatment and control measures. A technician was posted specifically for the sampling of suspected patients.
- Streamlining of the laboratory reporting system was done. The diagnosis was done using NS1 and Immunoglobulin methods. Earlier, the sample testing was once a week due to lesser load (NS1 was done on Tuesday and Immunoglobulin on Friday). With the rise in patient load, sampling was asked to be done on daily basis for early diagnosis and management. The NS1 was found to significant for first week of dengue, while the latter used to be significant after one week or so.
- The most important laboratory investigation is that of serial haematocrit levels and full blood counts. These investigations should be easily accessible from the health centre. Results should be available within two hours in severe cases of dengue.

Central Stores :

Intravenous fluids such as crystalloids, colloids and I/V sets were made available as per emergency requirement.

Pharmacy:

The adequate stocks of antipyretics and oral rehydration salts were maintained. Additional drugs (vitamin K1, Ca gluconate, NaHCO3, glucose, furosemide, KCl solution, vasopressor, and inotropes) for management of severe cases were also made available as per load.

Communication:

Facilities for easy communication, especially between secondary and tertiary levels of care and laboratories, including consultation by telephone were updated.

Blood Bank :

- Blood and blood components were made readily available to those who needed them. The daily assessment regarding the number of patients, their platelet counts and blood groups was done. Platelet count was repeated twice a day i.e. morning (8:00AM) and evening (4:00PM).
- The patients with platelet count of 50,000 or less were taken in to account for anytime need of platelets.
- Voluntary donors were mobilized.
- Patient relatives, doctors, staff members and students of the hospital were motivated for blood donation.
- Manpower was specifically rescheduled to manage the workload effectively.
- The patients with platelet count 10,000 or with bleeding problems were given the required transfusion.
- There was a corresponding increase in the demand and issue of blood and blood components (Table 2).

Discussion

Dengue virus infection is known to be endemic in India[3] . Our study highlights the vulnerability of Emergency blocks (in India) for earlier management of diseases even

in centers of excellence[4]. The situation in smaller hospitals can only be expected to be worse. Currently, there is a worldwide focus on improvement of quality of care in EMOPDs. So, a set of standard guidelines should be evolved for various levels of hospitals in India for handling infectious diseases and pasted in the EMOPD.

The study also emphasizes that not only healthcare systems have to be strengthened, but there is a need of combined approach from Government, Society and local board of health, and other providers to develop protocols and policies, which can respond to these kinds of events and would be able to handle future contingencies. The initial work up done by various authorities like MC, society and boards can be well imagined from the continuous annual rise in influx of dengue patients. From the Health care organization point of view, the hospitals itself can bear a load up to a limited threshold with its defined resources viz. manpower, material and infrastructure, so, under a new accreditation standard, EMOPDs and all departments must be prepared to handle an influx, or the risk of an influx, of infectious patients.

The major role of dengue management lies with public health bodies. There are no approved vaccines for the dengue virus[5]. Prevention thus depends on control of and protection from the bites of the mosquito that transmits it[6,7]. The primary method of controlling A. aegypti is by eliminating its habitats[8]. This is done by emptying containers of water or by adding insecticides or biological control agents to these areas, reducing open collections of water through environmental modifications, is the preferred method of control[8]. People can prevent mosquito bites by wearing clothing that fully covers the skin, using mosquito netting while resting, and/or the application of insect repellent (DEET being the most effective)[9].

The World Health Organization recommends an Integrated Vector Control program consisting of five elements: (1) Advocacy, social mobilization and legislation to ensure that public health bodies and communities are strengthened, (2) collaboration between the health and other sectors (public and private), (3) an integrated approach to disease control to maximize use of resources, (4) evidence-based decision making to ensure any interventions are targeted appropriately and (5) capacity-building to ensure an adequate response to the local situation[8]

There are no specific antiviral drugs for dengue, however maintaining proper fluid balance is important[10]. Treatment depends on the symptoms, varying from oral rehydration therapy at home with close follow-up, Paracetamol (acetaminophen) is used for fever and discomfort, to hospital admission with administration of intravenous fluids and/or blood transfusion[11] (patients presenting with unstable vital signs in the face of a decreasing hematocrit, and Packed red blood cells or whole blood are recommended, while platelets and fresh frozen plasma are usually not[12]. In the present study also, the treatment strategies opted were as per the treatment protocol of WHO and NVBDCP.

Print and electronic media need to be informed on day to day activities for control of dengue to build public trust. It is done by communicating openly and honestly, providing accurate and specific information about what people can do to make themselves and their community safer. This gives people a sense of control over their own health and safety, which in turn allows them to react to the risk with more reasoned responses[13].

Surveillance is an essential part of hospital control of infectious diseases. Many countries have tried to incorporate surveillance in their emergency medical services, and the role of national government in strengthening infectious disease control in an emergency has been debated[14].In India an Integrated Disease Surveillance Project (IDSP) has been implemented in many states to focus on early detection and control of spread of infectious diseases.

Hospital staff, doctors and nurses should be trained (short course/seminar) to diagnose cases of DHF, to recognize shock, and to provide proper management using WHO criteria and guidelines. Laboratory workers should be trained to do Haematocrit, CBCs and platelet counts or estimation by examination of peripheral blood smears and coagulogram. They should also be trained to collect blood specimens for serological diagnosis and/or virus isolation.

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Original Article

Intravenous esmolol is superior than sublingual nifedipine and intravenous lignocaine for attenuation of haemodynamic responses during laryngoscopy and endotracheal intubation

Utpal Kumar Ray[1], Prasanta Kumar Mandal[2]

Catacholamines released during laryngoscopy and endotrachial intubation (ETI) puts the patients at risk of development of various tachy arrythmias which have a deleterious effect on compromised cardiac functions. During the induction of general anaesthesia the two important events take place. One of them is laryngoscopy and another is endotracheal intubation. During laryngoscopy, the blade of the laryngoscope presses against the base of tongue and lifts up the epiglottis. This incidence gives rise to certain impulses to proceed through the vagus, the result being intense sympathetic stimulation. The cardioaccelerator nerve stimulation gives rise to tachycardia. The increase level of catecholamine gives rise to hypertension. Laryngoscopy produce more intense effects than endotracheal intubation in respect to cardiovascular system. Fifteen patients placed in each group received intravenous (IV) lignocaine (1.5mg), sublingual nifedipine (10mg) and IV esmolol (2mg/kg) 90 seconds,10 minutes 2 minutes before laryngoscopy and ETI respectively. Changes in heart rate, SBP, DBP, MAP RPR were recoded just after ETI and then after 1minute, 2minutes, 5minutes 10 minutes ETI. Results were compared with the control group (n=15, received no study medication). Intravenous lignocaine was not so much effective in countering the cardiovascular responses to laryngoscopy and ETI. Sublingual nifedipine produces a significant attenuation of SBP, DBP and MAP but it was unable to attenuate the pulse rate significantly. Intravenous esmolol is the best attenuator amongst the three drugs studied over here to the cardiovascular responses during laryngoscopy and intubation.

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Key words **: Laryngoscopy, endotracheal intubation, cardiovascular responses, lignocaine, esmolol, nifedipine.**

During the induction of general anaesthesia, the two important events take place. One of them is laryngoscopy and another is endotracheal intubation. During laryngoscopy, the blade of the laryngoscope presses against the base of tongue and lifts up the epiglottis. This incidence gives rise to certain impulses to proceed through the vagus, the result being intense sympathetic stimulation. The cardioaccelerator nerve stimulation gives rise to tachycardia. The increase level of catecholamine gives rise to hypertension. Laryngoscopy produce more intense effects than endotracheal intubation in respect to cardiovascular system[1,2].

The changes recorded are a rise in systolic blood pressure by about 30-50 mm of Hg, in diastolic pressure by about 20-30 mm of Hg, thereby increasing the mean arterial pressure. Heart rate increases by about 20-40 beats per minute (BPM) and thus increasing rate pressure product, an index for myocardial oxygen consumption. Various cardiac dysrhythmias, apart from sinus tachycardia or bradycardia, do occur in 5-10% of patients, usually are benign and transient. The sympathoadrenal stimulation may prove detrimental to the health of certain group of patients. Patients with ischaemic heart disease may have acute myocardial infarction. Patients with Ionotropically compromised heart increases the heart rate and thus lapse into heart failure. Patients with aneurysm in the cerebral vessels may have hypertensive haemorrhage in the brain. So to prevent these casualties, the sympathoadrenal system stimulation accompanying laryngoscopy and intubation must be obtunded.

This observations led to use of different techniques and attenuate the cardiovascular responses to laryngoscopy and endotracheal intubation like use of deeper plain of anaesthesia (both local and intravenous), narcotics, beta adrenoceptor blockers, vasodilators etc with various degrees of success. But no single method has gained wide spread acceptance because each method has its own disadvantages. Many newer studies are still being carried out with reevalu-

Department of Anaesthesiology, Murshidabad Medical College & Hospital, Berhampore 742101
[1]DA, MD (Anaesthesiol), Associate Professor,
[2]MS (Ortho), Associate Professsor, Department of Orthopedics, Bankura Sammilani Medical College, Bankura 722102 and Corresponding author

ation of older ones. With this Idea, an endeavour has been made to evaluate IV lignocaine, sublingual nifedipine and IV esmolol can modify the cardiovascular response to direct laryngoscopy and endotracheal intubation.

Material and Methods

The present study was carried out in the Department of Anaesthesiology, Murshidabad Medical College & Hospital and Department of orthopedics,BS Medical College, Bankura between April 2016 to July 2017. Subjects were selected amongst those were selected amongst those were put for surgery under endotracheal anaesthesia. Sixty patients were randomly chosen for this study. They were of both sexes. Their age ranged from 18 years to 50 years and weight ranged from 40 kg to 70 kg. The patients were carefully selected according to the American Society of Anaesthesiologist Classification and were in the status I & II category. The patients were selected from the general Surgical and orthopedic ward of Murshidabad Medical College&Hospital and BS Medical College & Hospital, Bankura. The procedure were fully explained to them and their written informed consent was obtained.

A detailed history was taken including the history of present and past illness, personal history, family history, past history of any operation and anaesthesia including history of drug intake and drug allergy. Clinical examination included measurement of Height, Weight, Nutrition, Pulse, Blood Pressure, Temperature, Anaemia, Jaundice, Cyanosis, Clubbing and edema. A Careful Clinical Examination of cardiovascular, respiratory, nervous, gastrointestinal and genitourinary system was done. Pre-operative investigations incuded Routine Examination of Blood – Total and differential count of white blood cell, Erythrocyte sedimentation rate, Haemoglobin, Urine – Macroscopic and Microscopic Examination, Stool – Macroscopic and Microscopic Examination, Blood Sugar (fasting and post-prandial), urea, creatinine, Serum Electrolytes – Na^+, K^+, and chloride, Chest X-ray (PA View) and 12 lead ECG.

None of the patients included in this study who have any history of respiratory, cardiovascular, hepatic, renal, endocrinal and metabolic disorders. Their mutritional status was found to be good. The patients has no history of receiving any psychotropic, hypnotic, antihypertensive, antiarrhythmic, diuretic antidiabetic and steroid therapy. All patients waiting for surgery were examined thoroughly in the ward 2 days before the expected day of operation. This opportunity was also utilised for establishing a pleasant report with the patient and allaying his/her anxiety. Altered anatomy of the mouth and neck, particularly dental structure might be a problem to quick and smooth intubation and any such patient was excluded from the study.

All the patients received tablet diazepam 10 mg at bed time on the night before operation. In the ward in the morning of operation, about two hours before induction of anaesthesia, pulse rate, systolic and diastolic pressure were measured and tablet diazepam (10 mg) was given orally.All the patients received Injection Glycopyrrolate (0.3 mg) Intramuscularly half hour before operation.Then the subjects were brought to the operation theatre and they were rested on the operation table for 5 minutes in a calm and quiet atmosphere to get them accustomed with the new environment.The subject were monitored for pulse rate (PR as beats per minute) by palpation of radial artery and for systolic and diastolic pressure (SBP and DBP respectively in mm of Hg) with the help of a mercury sphygmomanometer. After final checking of the subjects, Dependable intravenous channel was instituted. Pulse and Blood pressure were recorded which acted as a preoperative base line value (Before study drug administration).

Altogether sixty subjects were studied. They were placed randomly into four groups, each contains 15 subjects. The groups are –

Group – 1 : Control group – received none of the three drugs under the study

Group – 2 : Received intravenous lignocaine 1.5 mg/kg, 90 seconds before induction of anaesthesia.

Group – 3 : Received sublingual nifedipine (10 mg), 10 minutes before induction of anaesthesia.

Group- 4 : Intravenous esmolol (2mg/kg) 2 minutes before induction of anaesthesia.

In all the four groups, pulse rate and blood pressure were recorded before study drug administration which has been denoted as pre-induction value (Basal value).The patients were preoxygenated with 100% oxygen for 5 minutes from a Boyle's machine via a face mask and mapleson A system. Anaesthesia was induced 90 seconds after lignocaine, 10 minutes after sublingual nifedipine and 2 minutes after esmolol. Anaesthesia was induced with intravenous thiopentone (5 mg/kg of body weight) followed by suxamethonium (1.5 mg/kg of body weight) with proper care and monitoring. After full relaxation, laryngoscopy was done with a MaCintosh laryngoscope to expose the glottis properly and intubation was carried out in one attempt. The calf of endotrachel tube was inflated. Pulse and blood pressure was recorded which denoted as 'O' time (just after laryngoscopy and intubation). Blood pressure and pulse rate was taken 1, 2, 5 and 10 minutes after laryngoscopy and intubation (the 'zero' time). Maintenance of anaesthesia was carried out with nitrous 67%, oxygen (33%) injection Vecuronium 0.08% mg/kg and injection pethidine (1 mg/kg) intravenously. At the End of Surgery, the subjects were reversed from the residual relaxant effect of non-depolarizing muscle relaxants as necessary. During the whole period, the subjects were carefully observed for any untoward effects and specially for those which might be due to lignocaine, nifedipine and esmolol.

Results

In the present study sixty adult patients from both the sexes were divided into four groups. Group 1 served as control, Group 2, Group 3 and Group 4 were pretreated with intravenous lignocaine (1.5 mg/kg), sublingual nifedipine (10 mg) and Intravenous esmolol (2 mg / kg) respectively.

In all the groups the patients were between 18 to 50 years. The mean age was 36.67±3.12 years in group 1, 31.67±2.53 years in group 2, 39.93±2.89 years in group 3 and 38.80±2.45 in group 4.).Of the total 60 cases, twenty one were female and thirty-nine were male. All of them were in good nutritional status and free from systemic diseases. The patients in Group 1 had a mean weight 55.73 kg with a range from 40 kg to 70 kg. and in Group 2 was 52.67 kg. from 40 kg to 68 kg. The average weight in group 3 was 56.27 kg (range 44 kg to 70 kg), in Group 4 was 53.40 kg (range 45 kg to 68 kg).

There was an increase of pulse rate in all the groups of patient just after laryngoscopy and endotracheal intubation and 1 minute after intubation. At time 3, pulse rate was highest in group 1 (20.79%) and lowest in Esmolol group. When compared to basal value this increase was highly significant in all the groups ($p<0.01$). At time 4, the increase of pulse rate was highest in control group (15.73%) and lowest in esmolol group (6.28%) thereafter, the pulse rate decreases gradually. In control group, pulse rate returns to baseline value at 10 minute after intubation (Time 7). In lignocaine (Group 2) pulse rate returns to base line value at 5 minute after intubation and in group 4, pulse rate returns to base line value at 2 minutes after intubation and at 10 minute it goes below the basal level which is statistically significant ($p<0.01$).

Just after laryngoscopy and intubation, there was a peak increase of systolic bood pressure in all the groups. This increase was highest in group 1 (13.22%) and lowest in group 4 (6.12%). When compared to the control group of patients, lignocaine produce no significant change but nifedipine and esmolol produced a significant decrease of systolic blood pressure at 1 minute after intubation. With nifedipine and esmolol, the systolic blood pressure returns to the basal value within 1 minute after intubation and at 5, 10 minutes it comes down below the basal level which is statistically significant ($p<0.01$). In group 1, the systolic blood pressure comes down to the basal level at 10 minute and in lignocaine group at 5 minutes after intubation.

There was a peak increase of diastolic pressure just after laryngoscopy and intubation (Time 3). This Peak increase was highest in control group (15.63%) and lowest in esmolol group (6.10%). This increase was highly significant in all the groups when compared to basal value. When compared to the control group of patients Nifedipine and esmolol produce no significant change at 1 and 2 minutes after intubation. But there is significant decrease of diastolic pressure at 5 and 10 minutes after intubation. In group 2, these is no significant change of diastolic pressure at Time 2, Time 5 and Time 6 but there is significant decrease of pressure at 10 minutes after intubation ($p<0.01$).

There was peak increase of mean arterial pressure just after laryngoscopy and intubation (Time 3). This increase was highest in control group (14.54%) and lowest in esmolol group (6.11%). This increase was 10.23% in lignocaine group and 7.43% in Nifedipine group. This increase was highly significant in all the groups when compared to basal value ($p<0.01$).When compared to the control group of patients, lignocaine produced no significant change at 2 and 5 minutes after intubation. But at 5 and 10 minutes both Nifedipine and esmolol produced a significant decrease of mean arterial pressure (MAP) ($p<0.01$).

There was peak increase of Rate-pressure product just after laryngoscopy and intubation (Time 3) in all the groups. This increase was highest in control group (36.87%) and lowest in esmolol group (16.54%). This increase was highly significant in all the group ($p<0.01$). When compared to the control group of patients lignocaine produced no change at 5 minutes but in Nifedipine and esmolol group, no significant change found at 2 minutes after intubation. At 10 minutes after intubation, there is statistically significant decrease of rate-pressure product in all the groups except control groups. Sublingual Nifedipine was unable to attenuate the pulse rate but it produced a significant attenuation of systolic, diastolic and mean arterial pressure. More-over it produced statistically significant fall of pressure throughout the study period which is unwanted.

Intravenous lignocaine produced significant rise of pulse rate and blood pressure just after laryngoscopy and intubation (Time 3), 1 and 2 minutes after intubation (Time 4 and Time 5). Pulse rate and blood pressure comes to the basal level at 5 minutes after intubation. Significant decrease of blood pressure occurs at 10 minutes after intubation (Time 7, $p<0.01$).Intravenous esmolol was able to attenuate the pulse rate, systolic, diastolic and mean arterial pressure throughout the study period. Though there was significant drop of pressure at 5 and 10 minutes after intubation but it was not to he extent of Nifedipine.

Discussion

Endotracheal intubation has become the mainstay of modern anaesthesia due to various reasons like maintenance of good airway, prevention of aspiration, better oxygenation and laryngoscopy and tracheal intubation leads to reflex cardioacceleration stimulation, leading to an increase in systemic arterial pressure and heart rate.In modern anaesthesia, endotracheal intubation is essential for balance anaesthesia and for respiratory resuscitation measures in intensive care unit.

Bursstein (1950) suggested that these changes are due to an increase in sympathetic discharge via cardioaccelerator fibres.

The reflex cardioacceleration during laryngoscopy occurs due to laryngoscope-blade pressing on the base of the tongue and raising the epiglottis. The afferent path of the reflex is through the sensory fibres of the vagus and efferent is traveling through the cervical sympathetic nerves.

The increased sympathetic activity caused by stimulation of the upper respiratory tract has been supported by the observation that increase in arterial pressure during endotracheal intubation is associated with an increase of plasma nor-adrenaline level (Russel, W J 81)[3]. The initial rise of blood pressure and pulse rate is due to laryngoscopy and later an slight more increase is due to intubation. After intubation there is gradual return of blood pressure and pulse rate to pre-laryngoscopic value. This is probably due to the fatigue of the receptor.

The overall effect of inhaled anaesthetic is decrease in cardiac output and systemic vascular resistance. The inhaled anaesthetics are direct and potent depressants of myocardial contraction (Miller RD, '90). [Anaesthesia,4th edition, 1994][4].

Various methods have been used to attenuate the cardiovascular responses due to endotracheal intubation. These methods include deepening of the plane of anaesthesia (King BD '51. Prys – Roberts, '71), topical anaesthesia of laryngopharynx and Epiglottis (Delinger JK, '74, Stoelting RK '77, '78)[5,6,7]. Fentanyl and alfentanyl (Martin DE, '82, Black TE, '84). produce significant attenuation of cardiovascular response during intubation[8,9].

The effect of intravenous and oral practolol in hypertensive patients showed a significant attenuation of cardiovascular responses following laryngoscopy and intubation (Prys-Roberts '73).

The effect of esmolol, a new ultrashort acting beta blocker with an elimination half life only nine minutes, on the attenuation of cardiovascular responses to laryngoscopy was found to be much satisfactory (Achola KJ '88)[10].

Intravenous lignocaine 1.5 mg/kg 90 seconds before laryngoscopy and viscous lidocaine 25 ml (2%) given as mouth wash 10 minutes before laryngoscopy were equally protective but former seemed to be more logic choice (Stoelting RK, '77). But viscous or IV lignocaine were of no value when laryngoscopy is of very short duration (less than 15 seconds) (Stoelting RK '78)[11].

In 1979, Stoelting RK concluded that a single rapid intravenous injection of sodium nitroprusside (1 or 2 microgram/kg) is a practical pharmacological method to attenuate the blood pressure increase during direct laryngoscopy and tracheal intubation[12].

For attenuating the hypertensive and tachycardia response during endotracheal intubation, various other agents have been used such as metoprolol (Magnusson J '88), labetolol (Roelopse JA, '87), Magnesium sulphate (Allen RW, '91), captopril blocks the pressure response and tachycardia. The methods may them selves carry some additional risks and the drugs used may be long acting or have undesirable side effects[13,14]. The present study was carried out to observe the changes in arterial pressure, heart rate, Mean arterial pressure and Rate trachea and to compare the ability of IV lignocaine, sublingual Nifedipine and IV esmolol to obtund these responses.

Lignocaine causes peripheral vasodilation and myocardial depression. Lignocaine in plasma concentration 2-5 microgram/ml causes mild peripheral vasodilation with slight or no changes in myocardial contraction, diastolic filling and cardiac output. Lignocaine can accelerate the ventricular response during atrial flutter. It should be used cautiously in the treatment of supraventricular tachycardia during anaesthesia. Lignocaine can also cause seizures. Rapid IV Injection of lignocaine may cause cardiovascular collapse in susceptible patients. Following an concentration declines rapidly with a redistribution half life of about 10 minutes and elimination half life of about 2 hours (Roelepse, JA '87)[15].

Nifedipine inhibits the passage of calcium through the voltage-gated membrane channel of vascular smooth muscle and cardiac muscle. It reduces the available intracellular calcium and the muscle to relax.

It is the most potent vasodilator and can cause hypotension and faintness. Conventional Nifedipine has been used together with antihypertensive drugs that attenuates adrenergic responses. Reflex cardiac stimulation precipitating angina or myocardial infarction is rare because of the concomitant coronary vasodilatation of the drug. It is effective both in angina and hypertension.

Esmolol is a B_1 selective antagonist with a very short duration of action. It's elimination half life being 8 minutes. It's peak of action within 8-9 minutes and its activity ceases within 15-20 minutes after stoppage of the drug. It is metabolized by red cell esterase [DR Laurense, PN Bennett: Clinical Pharmacology, 1994][16].

In the present study sixty adult patients from both the sexes were divided into four groups. Group 1 served as control, Group II, Group III and Group IV were pretreated with intravenous.

Lignocaine (1.5 mg/kg), sublingual nifedipine (10 mg) and Intravenous esmolol (2 mg / kg) respectively.Increse in arterial pressure and heart rate caused by laryngoscopy and ETI was first described by King *et al*[5]. Rise of pulse rate after laryngoscopy and ETI was highest among control group in our study Prior administration of esmolol was most effective in blunting this rise of pulse rate. Intravenous esmolol was able to attenuate he pulse rate, SBP, DBP, and MAP through the study period.Though there was significant drop of pressure at 5 and 10 minutes after intubation but it was not to the extent of nifedipine. This observation was similar to the previous studies[11]. Other also reported that various beta blockers (like metoprolol, labetelol) have got the similar effects on pulse rate following laryngoscopy and ETI[13,15]. Sublingual nifedipine and esmolol effectively blunted the rise of SBP, DBP and MAP following laryngoscopy and ETI in our study. Sublingual nifedipine was unable to attenuate the pulse rate but it produced a significant attenuation of SBP, DBP and MAP. Moreeve it produced statistically significant fall of pressure throughout the study period which is unwanted. This was similar to the study results reported by Korpriva *et al* who used for reduction of heart rate but showed no effect on cardiac output and MAP[17].

Intravenous lignocaine produced significant rise of pulse rate and blood pressure just after laryngoscopy and intubation (Time4 and Time5) Pulse rate and blood pressure comes to the basal level at 5 minutes after intubation. Significant decrease of blood pressure occurs at 10 minutes after intubation ($p<0.01$, Time7). This findind is similar to other previous studies[7,18].

Conclusion

Laryngoscopy and intubation of trachea often evokes cardiovascular responses characterized by an increase of arterial pressure and heart rate and disturbance of cardiac rhythm. Usually these transient change have no deleterious effect in healthy patients, but in patients with altered tone in cardiovascular system, these changes may provoke life threatening consequences. The present study compares the efficacy of intravenous lignocaine, sublingual Nifedipine and intravenous esmolol for attenuation of cardiovascular responses during laryngoscopy and endotracheal intubation.

Analyzing the different data obtained from this study it was found that intravenous lignocaine was not so much effective in attenuating the cardiovascular responses to larygoscopy and intubation.

Sublingual Nifedipine produce a significant attenuation of systolic, diastolic and mean arterial pressure but it was unable to attenuate the pulse rate satisfactorily. At the same time, there is significant fail of pressure during the study period which is unwanted.

In the esmolol group, both pulse rate and arterial pressure showed a significant rise just after laryngoscopy and intubation. But two minutes after intubation the rise was not statistically significant in comparison to control group. Esmolol could check the rise both pulse rate and blood pressure at 2 minutes after intubation.The action of the easily controllable and reversible. It seems that esmolol is avery selective and appropriate answer to the problem of short time pressure response to laryngoscopy and endotracheal intubation.

From the present study, it is concluded that intravenous esmolol is the best attenuator amongst the three drugs studied over here to the cardiovascular responses during laryngoscopy and intubation.

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Observational Study

A study of incidence of gastric polyps in Upper GI Endoscopy, Histopathologic Features and Management options

Asit Kumar Sethi[1], Pradipta Kumar Mohapatra[2]

In the era of minimal invasive procedure with the increasing use of endoscopy[13], visually discernible abnormalities, such as polyps in the gastrointestinal tract, are encountered more often. Gastric polyps most frequently originate in the mucosa but encompass a broad spectrum of pathologic conditions that may even be submucosal or extrinsic. Found in 6% of upper endoscopies[5], gastric polyps are a heterogeneous group of epithelial and subepithelial lesions that can vary in histology, neoplastic potential, and management. Even though most are asymptomatic (>90%), larger polyps may present with bleeding, anemia, obstruction, or abdominal pain. Most have no risk of cancer, but there are certain subsets of polyps with malignant potential, necessitating further endoscopic treatment and/or periodic surveillance. These polyps are typically identified histologically because they have no reliable distinguishing endoscopic features. As many gastric polyps have similar endoscopic appearances, their classification depends on the histologic compartments from which they arise (ie, epithelial, hamartomatous, or mesenchymal). [*J Indian Med Assoc* 2018; 116: 20-2]

Key words **: Submucosal or extrinsic, subepithelial, hamartomatous.**

Histopathological Types of Gastric Polyp :

- **Epithelial Polyps :** Epithelial polyps are the most commonly encountered gastric polyps. They include fundic gland polyps (FGPs), hyperplastic polyps, and adenomatous polyps.
- **Fundic Gland Polyps :** FGPs are one of the most common polyps[3] found in the stomach (47%), observed in 0.8% to 23% of all endoscopies.
- **Familial Adenomatous Polyposis and Fundic Gland Polyps :** FAP is an autosomal dominant disorder characterized by numerous epithelial-derived polyps located throughout the gastrointestinal tract, most commonly in the colon. This condition is caused by a germline mutation of the adenomatous polyposis coli (APC) tumor suppressor gene.
- **Hyperplastic Polyps :** The hyperplastic polyp is the second most common gastric polyp after the FGP. A common misnomer for this polyp is inflammatory polyp, a term that should be discouraged because it can be confused with inflammatory fibroid polyp (IFP), which is managed much differently. Hyperplastic polyps are usually sessile or pedunculated, are less than 2 cm in diameter, and typically occur in the antrum, although they can arise anywhere.
- **Adenomatous Polyps :** Gastric adenomas, or gastric polypoid dysplasia, are true neoplasms and precursors to gastric cancer. Although commonly seen in countries with high gastric cancer rates (eg, Korea, Japan, and China), they also account for 6% to 10% of all gastric polyps in Western populations. Histologically, they are classified similarly to colon adenomas with tubular, villous, and tubulovillous distinctions. Frequently solitary, they are most commonly found in the antrum but can be located anywhere in the stomach. Endoscopically, they are often fat or sessile rather than pedunculated and can range in size from a few millimeters to centimetres.

Table 1 — *UGIE finding of Gastric Polyps*

Site of Polyp		Types of Polyp		No of Cases
		Sessile	Penduculated	
Fundus	Single		2	2
	Multiple	1	2	3
Body	Single	2	10	12
	Multiple	0	7	7
Antrum	Single	4	24	28
	Multiple	1	2	3
D1	Single	0	1	1
	Multiple	1	5	6
D2	Single	0	0	0
	Multiple	0	4	4

- **Juvenile Polyps and Juvenile Polyposis Syndrome :** Juvenile polyps[2] are mucosal tumors that consist primarily of an excess of lamina propria and dilated cystic glands; therefore, they are classified as hamartomatous polyps. Occasionally, they are referred to as inflammatory or retention polyps due to the appearance of distended, mucus-filled glands, inflammatory cells, and edema. Juvenile polyps are typically solitary pedunculated lesions in the antrum and range from 3 mm to 20 mm. **A:** Juvenile polyps are hamartomatous polyps and typically found in the antrum. Solitary polyps have hamartomatous or inflammatory components. **B:** Juvenile polyps are less specific in their histology than Peutz-Jeghers polyps and are sometimes.
- **Mesenchymal Polyps:** Mesenchymal lesions cover a broad spectrum of mesodermally derived tumors. These polyps can be mucosal or submucosal in location but are typically situated underneath the surface epithelium, imparting a more nodular than polypoid appearance. Given their deep location, these lesions should be further evaluated by endoscopic ultrasound (EUS)[14] and tissue acquisition. Select common mesenchymal polyps covered herein include IFPs, GISTs[11], leiomyomas, and granular cell tumors.

Department of Surgery, SCB Medical College, Cuttack 753001
[1]MS, FIAGES, FMAS, Assistant Professor
[2]MS, FIAGES, PG DMCH, Consultant Surgeon, Shanti Memorial Hospital, Cuttack 753001 and Corresponding author

Management of Gastric Polyps :

- **Fundic polyp :** The discovery of gastric polyps during an endoscopic[3] examination of the stomach is a relatively common occurrence for gastroenterologists[1]. In fact, a diverse array of polyps and polypoid lesions are found in the stomach. However, there is a paucity of specific analytic and practical clinical guidance for the management of such lesions.

Management : Larger polyps (>1 cm) should be removed endoscopically, and if the patient is taking a PPI, discontinuation of the PPI should be considered. Although no guidance is offered regarding optimal intervals for follow-up examinations, regular surveillance[6] by endoscopy is recommended.

Key Point : When multiple fundic gland polyps are evident in younger patients[2], evaluation for familial polyposis should be considered.

- **Hyperplastic polyps :** Hyperplastic polyps are caused by an inflamed and often atrophic gastric mucosa. These polyps typically occur in the antrum and often in presentations of multiple lesions. They have a smooth, dome-shaped appearance. Hyperplastic polyps can be large in size, and patients may present with chronic blood loss or even gastric obstruction.

Management : Elimination of the underlying cause, such as H pylori infection, typically results in polyp regression. When encountered as isolated or polypoid lesions at gastrectomy sites, hyperplastic polyps have a low but defined neoplastic risk[7,9]. For this reason, large polyps must be completely excised[1]. In the absence of dysplasia, the optimal management of small polyps located at gastrectomy[17] sites was not defined.

Key Point : The diagnosis of a hyperplastic polyp of any size requires a full set of gastric biopsies to determine gastric mucosal characteristics for purposes of topographic mapping. If H pylori infection is present, eradication is warranted, and follow-up endoscopy is appropriate to confirm cure of the H pylori infection as well as regression of the remaining polyps.

- **Adenomatous Polyps :** Adenomatous polyps occur sporadically or in association with familial polyposis. Typically, these polyps are circumscribed and can be pedunculated or sessile in form. In addition, they can have dysplastic epithelium that does not invade the lamina propria.

Management : Endoscopic resection is appropriate, and surveillance follow-up at 1 year is recommended. Gastric mapping is useful to determine whether there is atrophic gastric metaplasia, which would be an indication for surveillance.

Key Point : A synchronous adenocarcinoma has been found in another area of the stomach in up to 30% of patients who have an adenomatous polyp. For this reason, careful inspection of the entire stomach is warranted when adenomatous polyps are identified.

- **Polyposis Syndromes :** Polyposis syndromes, which are characterized by the growth of multiple polyps, are rare and include juvenile polyposis, Cronkite-Canada syndrome, Peutz-Jeghers syndrome, and Cowden's disease. Hamartomatous polyps may be present in all of these syndromes. Adenomatous polyps[12], as mentioned, may be found in familial polyposis.

Management : There is no defined guideline for the care of patients who have familial polyposis[1], but it is suggested that endoscopic surveillance be performed at 30 years of age and at 3-year intervals. Patients who have large numbers of polyps should undergo surveillance annually. Juvenile polyposis has a lifetime associated risk for gastric cancer[14] of 15% to 20%, and gastric surveillance[8] is recommended at 1- to 2-year intervals.

Key Point : In Cowden's disease, there is no association with gastric malignancy. Instead, surveillance should focus on breast and thyroid cancer screening.

- **Inflammatory Fibroid Polyps :** Inflammatory fibroid polyps, also known as Vanek tumors[10], are rare, representing fewer than 1% of all gastric polyps. These tumors are rarely symptomatic but can be associated with bleeding or gastric outlet obstruction.

Management : Most inflammatory fibroid polyps are found incidentally and do not recur. No surveillance is recommended.

Key Point : Inflammatory fibroid lesions typically have massive eosinophilic infiltrates and are occasionally --and incorrectly - called eosinophilic granulomas.

- **Gastrointestinal Stromal Tumor :** Gastrointestinal stromal tumors (GISTs) make up 1% to 3 % of gastric neoplasms and occur more frequently in men than in women. GISTs[11] are typically located in the fundus. Because these lesions are submucosal, mucosal biopsy proves inadequate as a diagnostic assay in that results are typically normal. Endoscopic ultrasonography-guided biopsy

with fine-needle aspiration provides the best tissue sample for diagnosis. GISTs are categorized as having malignant potential ranging from low risk to high risk on the basis of polyp size and level of mitotic activity.

Management : All GISTs should be regarded as having neoplastic potential. Up to 50% of patients have metastatic disease (typically hepatic) on presentation. Surgical resection[16] is recommended for lesions larger than 2 cm. Endoscopic[4,15] resection is an option for smaller GISTs.

Key Point : GISTs have a unique immunostaining characteristic that allows a specific diagnosis: The stain for the KIT gene product CD117 is positive in 95% of cases. Endoscopic removal of GISTs is controversial because of reports of positive resection margins and tumor spillage.

- **Carcinoid Tumors :** There are 3 types of gastric carcinoid tumors. Type 1 carcinoid tumors account for 65% to 80% of all gastric carcinoids and are more common in women than in men. They are often associated with chronic autoimmune atrophic gastritis and pernicious anemia. Type 2 carcinoid tumors account for 3% to 15% of gastric carcinoids and are associated with Zollinger-Ellison syndrome and multiple endocrine neoplasia. Type 3 carcinoid tumors are sporadic, account for approximately 20% of gastric lesions, and occur more frequently in men than in women. Types 1 and 2 carcinoids are associated with the development of hypergastrinemia. These related carcinoids are typically multiple, broad-based, firm, yellowish lesions that are located in the fundus or gastric body. They tend to be smaller than 2 cm. In contrast, the sporadic type 3 carcinoids are typically single, prepyloric, and larger than 2 cm.

Management : The overall prognosis depends on the type of carcinoid encountered. Local excision[1] is recommended, if possible. Type 1 carcinoids rarely metastasize. However, antrectomy should be considered if multiple lesions are present. Type 2 carcinoids should be managed by endoscopic polypectomy followed by regular surveillance if the underlying gastrinoma cannot be removed. Type 3 lesions have a propensity for invasion and metastasis. Gastrectomy is the therapy of choice, although the 5-year survival rate is still less than 50%.

Key Point : The carcinoid syndrome when associated with gastric carcinoids is present almost exclusively in patients with type 3 lesions.

Conclusion :

Gastric polyps are a common finding during routine endoscopy. Despite the fact that more than 90% are asymptomatic and do not have malignant potential, a subset of gastric polyps require further intervention, and histologic evaluation is necessary to determine the type of polyp and the presence of dysplasia. The identification of such polyps requires histologic evaluation and may involve additional diagnostic investigative techniques, such as tandem biopsies, immunohistochemistry staining, EUS, and EUS-assisted tissue acquisition. Furthermore, it is essential for gastroenterologists to provide full endoscopic and clinical information to the pathologist to reach a proper diagnosis, as many conditions have similar histologic characteristics.

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Observational Study

Economic burden for management of community-acquired pneumonia in children below 5 years in India

Canna J Ghia[1], Shalaka A Marfatia[2], Tushar H Maniar[3], Baratu B Bhaisara[4], Craig Roberts[5], Gautam S Rambhad[6]

For reporting direct and indirect costs for managing community-acquired pneumonia (CAP) in children <5 years in India,we reviewed medical records of 532 children with respiratory conditions hospitalized in public hospital (PBH) and private hospital (PVH) between 2012 and 2014. Inpatient costs were estimated from discharge records; outpatient costs were estimated using physician and parent surveys. Cost analysis was performed in 169 children with CAP (PVH: 102 [60.35%]; PBH: 67 [39.64%]). Mean duration of hospitalization was shorter in PVH than in PBH (5.87 versus 7.97 days). Average per-episode hospitalization cost was almost 7 times higher in PVH than in PBH. Mean outpatient direct and indirect costs were 10,688 ($148) and 9,286 ($129).Sick-time costs in PVH and PBH were 9,286 ($129) and 3,118 ($43). High costs of CAP management are attributed to hospitalization and diagnostic test costs. Pneumococcal vaccination may reduce these costs.

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***Key words* : Community-acquired pneumonia, cost analysis, under 5 children.**

Pneumonia is the single largest cause of infection-related deaths in children worldwide, accounting for 16% of all deaths in children <5 years old (under 5)[1]. Community-acquired pneumonia (CAP) is most frequently caused by Streptococcus pneumoniae, followed by Haemophilus influenzae and Mycoplasma, Chlamydia, and Legionella spp[2]. Farooqui *et al* estimated 3.6 million episodes of severe pneumonia and 0.35 million pneumonia deaths in under 5 in 2010 in India[3]. CAP frequently causes hospitalization in under 5 in India[4].

Pharmacotherapy includes oral antibiotics such as macrolides (azithromycin) or ß-lactams (amoxicillin) for outpatients without comorbidities for 5 days. Hospitalized patients in non-intensive care units (ICUs) are recommended a ß-lactam (cefotaxime, ceftriaxone, or amoxicillin-clavulanic acid) plus a macrolide for 7 days.Treatment can be continued depending on etiologic agents and comorbidities[5].

Direct costs for CAP management include medicines, investigations, consultation, and hospitalization duration; indirect costs include transportation, food, child care, lost time and income of parents/care givers. Nursing cost[6], laboratory investigations, and oxygen therapy affect costs[7]. Choice of initial antibiotics influences hospitalization duration; inappropriate therapy results in additional costs[8]. Saha *et al* (2017) showed that compared with indirect costs, direct costs were maximal. Among different drugs, antibiotics were financially the most burden some on patients and their families[9].

We retrospectively assessed clinico-demographics and resource utilization (including direct and indirect costs) in under-5with newly diagnosed CAP.

Materials and Methods

We retrospectively reviewed medical records of under-5 hospitalized in Dr Balabhai Nanavati Hospital (private hospital, PVH) and Dr RN Cooper Municipal General Hospital (public hospital, PBH), Mumbai, India, between January 2012 and 2014. We conducted the study in compliance to protocol and all relevant regulatory guidelines after obtaining institutional ethics committees' approval.

Children with a new pulmonary infiltrate associated with any of following symptoms—new or increased cough, fever or hypothermia, leukocytosis, left shift, or leukopenia—with complete medical records and confirmed CAP diagnosis (Fig 1) were included. Children with hospital-acquired pneumonia, asthma, chronic obstructive pulmonary disease, bronchiolitis, or common cold were excluded.

Data on demographics, comorbidity, diagnostic tests, medications, hospitalization duration and ICU stay, and

[1]MD, Senior Medical Advisor Pfizer Limited, Mumbai 400051 and Corresponding author
[2]MS, MPH, Principal, pharm EDGE, Health Economics and Outcomes Research, Mumbai 400063
[3]MBBS, MD, Consultant Pediatrics, Nanavati Hospital, Mumbai 400065
[4]MBBS, MD, Consultant Pediatrics, Cooper Hospital, Mumbai, India 400065
[5] Pharm D, MPA, MBA AVP, Merck & Co, Inc.*
[6]MD, Vaccines Medical Lead, Pfizer Limited, Mumbai 400051
*(*Dr Roberts was an employee of Pfizer Inc. at the time of this study)*

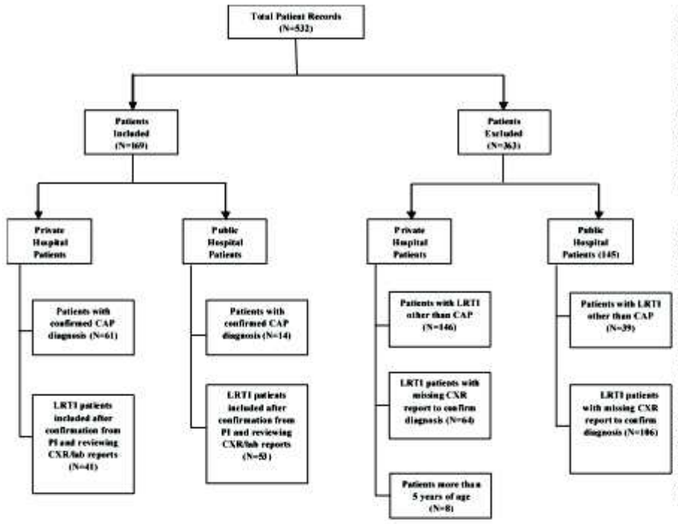

Fig 1 — Flow Diagram for Study Subjects
CAP=community-acquired pneumonia; CXR= Chest X-ray; LRTI=lower respiratory tract infection; N=number of patients; PI=principal investigator

inpatient costs (from discharge records) were collected.

Outpatient data were collected by a self-administered survey from[5] leading pediatricians.Questionnaire items included resource use for laboratory tests (diagnosis and follow-up), physician visits, and pharmacotherapy. Total outpatient costs were estimated by multiplying average cost for each resource by its frequency. Sick-time costs associated with lost productivity (time off from work by parents/caregivers) were assessed through telephonic interviews regarding type of work, designation, organization, salary range, and paid leaves availed for nursing children.

Statistical analyses were performed using SAS© version 7.0. Continuous variables were summarized using mean, median, and standard deviation. Categorical variables were summarized by frequency. Multivariate log linear regressions were performed to understand if age, gender, and weight predicted total inpatient cost.

Results

Of 532 children,169 (31.76%) under 5 with confirmed CAP diagnosis were included: 102 (60.35%) from PVH and 67 (39.64%) from PBH (Fig 1).

Mean±standard deviation (SD) patient age was 1.95±1.45 years in PVH and 1.51±1.17 years in PBH. Most PBH patients were males (59.70%); equal gender distribution was observed in PVH. Mean±SD patient weight was more in PVH (9.95±3.91 *versus* 7.71±2.43kg) (Table 1).

Cough and fever were commonest reasons for hospitalization in both settings, followed by breathlessness (52.24%) in PBH. Primary diagnosis was unspecified pneumonia in most children (~93%) in both settings. Vaccination rate was higher in PVH patients (79.41% *versus* 65.67%) (Table 1).

Table 1 — *BaselineSociodemographic and Clinical Characteristics*

Characteristics	Private Hospital (N=102)	Public Hospital (N=67)
Age (years), Mean±SD	1.95±1.45	1.51±1.17
≥1 month (%)	1.96	1.49
1 month–1 year (%)	34.31	43.28
>1 year (%)	63.73	55.22
Weight (kg), Mean±SD	9.95±3.91	7.71±2.43
Gender (%) :		
Female	48.04	40.30
Male	51.96	59.70
Primary Reasons for Hospitalization (%) :		
Breathlessness	16.67	52.24
Chest Pain	0.98	-
Cough	94.12	95.52
Fever	91.18	94.03
Tachypnea	3.92	-
Wheezing	0.98	-
Other Reasons (%) :		
Chills	5.88	-
Cold	56.86	88.06
Rapid Breathing	0.98	-
Vomiting	15.69	-
Murmur	-	1.49
Primary Diagnosis of Pneumonia (%) :		
Mycoplasma	3.92	-
Viral	2.94	-
Bacterial	-	7.46
Other/unspecified	93.13	92.53
Vaccination (%) :		
Done	79.41	65.67
Unknown	16.66	10.44
Not done	3.92	23.88

Complete blood count and chest radiograph were primary diagnostics used in >90% under 5 admitted to both facilities. Mycoplasma pneumoniae immunoglobulin M (IgM) test was performed in 32.35% PVH patients compared with none in PBH. Blood culture was performed in 37.25% and 8.95% PVH and PBH patients, respectively. Sputum culture was performed in 13.43% PBH patients (Table 2).

PVH patients received linezolid (66%), azithromycin (25%), and amoxicillin/clavulanate (15%). Most PBH patients received amoxicillin/clavulanate (91%), followed by amikacin (16%) and ceftriaxone (10%).After discharge, 85% PVH patients continued antibiotics for 4.3 days (mean) compared with 54% PBH patients for 2 days (mean).

Table 2 — *Laboratory and Imaging Tests for Diagnosing Community-acquired Pneumonia*

Diagnostic Test	Private Hospital (N=102)	Public Hospital (N=67)
Laboratory Test (%) :		
Complete blood count	91.17	95.52
Blood culture	37.25	8.95
Sputum culture	1.96	13.43
Malaria	30.39	40.29
Mycoplasma pneumoniaeimmunoglobulin M	32.35	-
Dengue	7.84	4.47
Blood gas analysis	0.98	-
Imaging Test (%) :		
X-ray	92.15	95.52
Computed tomography	9.80	-
Other	17.64	-

Overall mean±SD hospitalization duration was shorter in PVH (5.87±3.50 *versus* 7.97±4.74 days), also if it was a general ward (4.63±2.18 *versus* 7.59±4.41 days). This trend was similar in PVH irrespective of routes of antibiotic administration—intravenous (6.91±5.13 *versus* 7.51±4.63 days), oral (5.22±3.60 *versus* 12 days), or both (5.41±2.42 *versus* 9.44±4.83 days). However, mean ICU stay was longer in PVH (0.75±2.67 *versus* 0.19±1.59 days).

Inpatient costs are provided in Table 3. Mean±SD diagnostics cost was approximately 4 times higher in PVH (4,750±5,513; $76±8) than in PBH (1,807±1,516; $29±24). No cost was incurred for hospitalization in general and other wards, physician visits, and consumables in PBH; mean cost for these activities was approximately 19,000 ($301) in PVH. Mean±SD inpatient cost per CAP episode was much higher for PVH patients (34,535±32,483; $553±520) than for PBH patients (4,934±7,254; $79±116).

Mean outpatient cost of treating a CAP episode was 10,688 ($148). Per caregiver interviews, sick-time cost for 9.5 days (mean) (PVH: mothers 5.5 days; fathers 4 days) of paid leaves was 9,286 ($129). Parents (mostly mothers) of under-5 in PBH availed an average 6 days of paid leaves amounting to 3,118 ($43) as sick-time cost.

Exploratory regression analysis demonstrated that age, gender, and weight did not significantly predict in patient cost in PVH; however, age (p=0.0014) and age and weight together (p=0.001) were associated with in patient cost in PBH.

Discussion

Our results provide insights into the economic burden of CAP management on families of under[5]. Mean inpatient cost was 7 times higher in PVH than in PBH and almost 3 times higher than mean outpatient cost. This finding corroborates with the estimates of Indian National Health Accounts reporting a household expenditure of 64,628 crores ($8976 million) on PVH compared with 8,193 crores ($1138 million) on government hospitals[10].

Patients' demographic and clinical characteristics were similar at both facilities, except for weight. Lower vaccination rate and higher breathlessness case numbers in PBH suggest parents' unwillingness to seek treatment unless symptoms worsen. Indirectly, this reflects parents' inabilityfor paying healthcare costs.

Both facilities used radiographic evidence (CXR) for diagnosis per the Indian guidelines[5]. Blood and sputum culture, M pneumoniae IgM test, and bacterial pneumonia identification tests were not performed in PBH. Of32.35% PVH children tested for M pneumoniae IgM, only 3.92% were positive. Per Indian CAP guidelines, this test need not be routinely performed[5]. An empirical treatment is recommended in children[11] since clinical features or laboratory and radiological investigations cannot reliably differentiate infections caused by atypical pathogens, bacteria, and viruses in children[12]. Identifying causal pathogens influences treatment choice and affects overall healthcare utilization (HRU) costs. We found a considerable expenditure on laboratory tests (4,750; $66) in PVH, increasing the overall economic burden on the families.

Compared with achieving late response in CAP patients, achieving early response (=4 days) decreases hospitalization duration, lowers ICU admission rate, shortens ICU stay, and causes lesser initial treatment modification or readmission[13]. Key contributors of CAP associated direct medical costs in India identified earlier were hospitalization duration[7]and antibiotic use[9]. Medicine cost

Table 3 — *Inpatient Costs Associated with Community-acquired Pneumonia*

Parameters	Private Hospital (N=102)		Public Hospital (N=67)	
	Cost Per Patient		Cost Per Patient	
Clinical Services, Mean±SD :				
Lab Tests	4750±5513	$70±77	1807±1516	$25±21
Non-lab Tests	1356±2224	$19±31	-	-
Imaging	2497±4530	$35±63	41±34	$0.57±0.47
Hospital Services, Mean±SD :				
Admission	187	$2.6	10	$0.14
Intensive care unit	2500±8708	$35±121	39±318	$0.62±5
General ward	9816±6325	$136±88	-	-
Other wards	1560±6062	$22±84	-	-
Physician visit	6464±5776	$90±80	-	-
Consumables	976±2019	$14±28	-	-
Medications	3829±5210	$53±72	3036±5810	$42±81
Surgical Services, Mean±SD :				
Surgeon's fee	207±1068	$3±15	-	-
Consumables	332	$4.6	-	
Other Services	61±198	$0.85±2.75	-	-
Average Cost	34,535±32,483	$480±451	4934±7254	$69±101

mostly (72%) contributes to total out-of-pocket payments (from 42% for inpatient care to 82% for outpatient care)[14]. We report similar findings regarding mean hospitalization duration (PVH: 5.87 days; PBH: 7.97 days) and medication costs (PVH: 3,829; $46 and PBH: 3,036; $42). Although physician visits, consumables, and general ward expenses are not charged in PBH, patients spend out-of-pocket for medicines and the Government incurs a considerable expenditure. A systematic review found that mean hospitalization duration for children with severe pneumonia was 5.8 (interquartile range [IQR] 5.3–6.4) and 7.7 (IQR 5.5–9.9) days in low- and middle-income countries and high income countries[15]. We found that hospitalization duration in PBH was equivalent (7.97 days) to that in high-income countries.

Cost burden of outpatient CAP management is less explored. We found mean outpatient cost was same for PBH and PVH (10,688; $148).Loss of work productivity and increased sick-time costs accounted for 20% and 38% of total cost in PVH and PBH, placing a considerable burden on parents/caregivers. Indian families spent ~10% of total household income on treatment of acute morbidities in children[16]. Mean direct nonmedical and indirect costs for severe pneumonia management were 0.5%-31% of weekly household income[15].

Various international and Indian guidelines recommend pneumococcal vaccination in children. Two pneumococcal conjugate vaccines (PCVs), PCV13 and PCV10, are licensed in India[17]. PCV13 is introduced from 2017 under Universal Immunization Programme of 5 states[18]. PCV13 has an acceptable safety profile in infants and toddlers, and covers most serotypes prevalent in India[19]. Thus, extensive coverage of PCV vaccination would prevent CAP-associated mortality and reduce hospitalization-associated economic burden.

Study limitations include small sample size, limiting generalizability of findings; self administered questionnaires for evaluating outpatient HRU cost, which may not represent actual expenditure; and the recall method for calculating caregiver's sick-time cost.Parents'/caregivers' reduced work performance (after returning to work) during children's recovery period was not assessed.

Conclusion :

HRU cost for CAP considerably consumes the monthly income of Indian families, irrespective of treatment settings. Definitive diagnosis and appropriate antibiotic cover may reduce hospitalization duration. Pneumococcal vaccination in under-5 may reduce overall economic burden of CAP management.

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Special Supplement on ENDOCRINOLOGY

Editorial

Dr. Dipanjan Bandyopadhyay
MD, Professor & Head, Department of Medicine, North Bengal Medical College, Siliguri
and Joint Guest Editor, JIMA

Dr Saptarshi Bhattacharya
MD, DM, Senior Consultant, Department of Endocrinology, Max Superspeciality Hospital, Delhi
and Joint Guest Editor, JIMA

Endocrinology : Scientific and societal

Endocrine disorders like diabetes, hypothyroidism and osteoporosis are widely prevalent. But these disorders very commonly remain undiagnosed and undertreated. The current issue of Journal of Indian Medical Association endeavors to increase awareness about these very common but neglected conditions.

Osteoporosis is a leading public health concern. Hip fractures, one of the most common variety of osteoporotic fracture, has a reported 1-year mortality as high as 58%. But the grim reality remains that many of the elderly patients who sustain osteoporotic fractures do not receive treatment for osteoporosis. At other times, they get treated with ineffective agents like calcitonin which has fallen into disfavor due to concerns regarding malignancy. The right perspective to approach a patient with osteoporosis is discussed in the article on osteoporosis. Vitamin D deficiency is another global public health problem and contributes partly to development of osteoporosis. Hypovitaminosis D can be treated by several doses and regimens but overzealous correction has also lead to the increased incidence of hypercalcemia and acute kidney injury. The article on Vitamin D deficiency in Indian context highlights the issues concerning diagnosis and management of this common clinical condition.

Primary hypothyroidism is another prevalent and mismanaged clinical condition. The treatment of this condition with thyroxine replacement though supposedly a straight forward proposition, it remains under or overtreated in almost 50% of patients as shown by studies. Besides, there are important differences in diagnosis and management of hypothyroidism in elderly population, that has been aptly elaborated in the article on hypothyroidism in elderly population. Hyperthyroidism represents the other spectrum of thyroid related disorders. The clinical presentation and treatment pattern in Indian setting has been elucidated in the observational study published in the issue.

The ever increasing burden of diabetes and its complications is not only a huge challenge for the affected individual and the treating physician but also for the society in general. Appropriate dietary approaches can prevent diabetes and there are early and encouraging signals that these may even reverse it in the initial stages. These preliminary findings require the rigorous scrutiny of clinical trials before they can be accepted as high quality scientific evidence. A controversial area in management of diabetes and obesity is use of artificial sweeteners. The review on artificial sweeteners critically analyzes scientific evidence regarding their usage. The editors are thankful to the team of eminent doctors for publishing the consensus statement on diabetic neuropathy in the current issue. The article on risk factors of diabetic nephropathy throws light on another common complication of diabetes. Early identification of these risk factors can prevent this grave complication. Cardiovascular mortality still accounts for two-thirds of death in diabetes and the recently published positive cardiovascular outcome trials might play a role in selection of the appropriate glucose lowering agent.

On the ever expanding horizon of medical information and the rising expectations from our fraternity, it is an appropriate endeavor for JIMA to dedicate this issue to Endocrinology. We hope our readers shall cherish reading the articles.

Observational Study

Presentation and management of Graves' disease — Experience from a tertiary care center in Eastern India

Subhodip Pramanik[1], Rana Bhattacharjee[2], Subhankar Chowdhury[3]

Graves' disease has varied presentation and preference for therapeutic modality varies from country to country. We report the presentation and mode of therapy we perform in a tertiary care center in Eastern India. This is a retrospective data of 60 patients with Graves' disease evaluated and treated at Institute of Post-graduate Medical Education and Research (IPGMER), Kolkata. Patients were recruited consecutively between March 2017 and May 2017. Baseline characteristics revealed median (±IQR) age of presentation 33.1±10.1 years, F:M ratio 2.3:1, median duration 7.7±6.8 months, 28% were overweight and 20 % were smoker. Most common mode of presentation was tremor (93%), followed by palpitation (86.6%), weight loss (85%) and hyperdefecation (25%). Overall 31 (51.6%) patients had eye signs and active eye disease was present in 5 (8.3%) patients. Only 30 patients were screened for glycemic status at disease onset and 12 (40%) were found to have dysglycemia. Diagnosis of Graves' was mostly done by clinical examination (57%), followed by Isotope studies (38%) and only 3 (5%) patients by Anti TSH receptor antibodies (TRAb). Majority of the patients (70%) underwent medical therapy alone, followed by radioiodine ablation (21.6%) and surgery done in 5 (8.3%) patients only. Average radioiodine dose was 11.9 ± 2.1 mCi and only 2 (13.3%) patient needed repeat dose. 2 patients out of 5 who underwent total thyroidectomy developed permanent hypoparathyroidism. A comprehensive overview of management of Graves' disease in Eastern India is described. There is high prevalence of dysglycemia but often not screened. Requirement of usage of TRAb is still minimal and restricted to special cases only.

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***Key words* : Hyperthyroidism, Radioiodine therapy, Diabetes in Graves.**

Graves' disease during its first recognition in 19th century was known for a cachexic look, enlarged thyroid gland, an accelerated heart rate, and ocular abnormalities[1].With gradual increase in understanding and awareness among doctors and patients, this disease is diagnosed at much earlier stage and thus the mode of presentation has changed. Again preference for diagnostic and therapeutic modality varies from country to country. Bartalena L *et al*[2] conducted a survey among endocrinologists in Europe, North America and Asia regarding the diagnosis and management strategy of Graves. Recently Hussain YS *et al*[3] reported real life data regarding epidemiology, management and outcomes of Graves' disease in United Kingdom. Diagnostic modalities include pathognomonic clinical findings (orbitopathy, dermopathy, acropachy, brui on thyroid gland auscultation), ultrasonograhy (increased vascularity), radioisotope scan (diffuse increased uptake) and Anti thyrotropin receptor antibody (TRAb) positivity[4]. In general, medical therapy is started to control thyroid hormone production and release, with an aim to relieve symptoms and to normalise thyroid hormone levels. Following failure of medical therapy or sometimes denovo, definitive treatment with either surgery or RIA is considered. However, good quality data information on short and long-term outcomes of treatment in consecutive cohorts of patients with Graves' disease from India is lacking.

Department of Endocrinology, IPGMER, Kolkata 700020
[1]DM, Senior Resident and Corresponding author
[2]DM, RMO *cum* Clinical Tutor
[3]DM, Professor and Head

Materials and Methods

This is a retrospective survey which included patients diagnosed as Graves' disease from Endocrinology outpatient department (OPD) Institute of Post-graduate Medical Education and Research (IPGMER), Kolkata. Sixty patients of documented Graves' disease on at least 3 month follow up were included consecutively in this survey.Data on these patients such as demographics (age, gender, BMI-body mass index and smoking status), presentation, biochemical features at onset (TSH -Thyroid Stimulating Hormone, FT4 - Free Thyroxine, T4-Total T4, T3 -Triiodothyronine, TRAb - TSH Receptor Antibody, FPG-Fasting plasma glucose, PPPG-Post prandial plasma glucose), imaging study if any, mode of treatment, outcomes and current status of disease was collected from previous documents. Those having incomplete data or those with unclear diagnosis were excluded from the study.

The reference ranges for normal values for the various laboratory investigations include 0.4–4 mIU/L for TSH, 0.8–1.9 ng/dl for FT4, 4.5-12 µg/dlfor T4 and80-180 ng/dl for T3. Thyroid function was estimated mostly in our institute by the electrochemiluminescence (ECL) technique using commercially available kits from Siemens Diagnostics (Germany) with Immulite 1000 analyzer. TRAb was done from outside lab as this is not available in our hospital, so the method and interpretation was heterogeneous. Fasting plasma glucose (FPG) and post prandial plasma glucose (PPPG) reports were traced to determine glycemic status and it was defined as per American Diabetes Association (ADA) 2018 criteria[5].

The outcome of initial medical treatment was defined from biochemical response (FT4 and TSH) and clinical examination and recorded as follows: Controlled disease—normalization of biochemistry whilst on ATDs or within 1 month of withdrawal of ATDs, Disease remission—patients whose disease was controlledwith ATDs and where control was maintained for at least a month after withdrawal of medical treatment, Uncontrolled disease—persistently abnormal biochemistrydespite ATDs or intolerant to ATDs.

Statistical Package for the Social Sciences (version 14.0, SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Results on continuous measurements were presented on mean ± standard deviation (for scewed data, it was presented as median ± interquartile range--IQR) and results on categorical measurements were presented in number (N) and percentage (%). Given the observational nature of the study, approval from the regional ethics committee or individual patient consent was not deemed necessary.

Results

Consecutive 60 patients were included in this survey. Baseline characteristics revealed age of presentation 33.1 ± 10.1 [median (±IQR)] years, 4 (6.6%) patients were less than 18 years of age. Female: Male ratio was 2.3: 1 and median duration of symptoms was 7.7 ± 6.8 months. In 55 out of 60 patients had goiter Ib or more (91.6%), although only 27 (49%) patients actually noticed it. Median ± IQR BMI (in kg/m^2) was 20.7 ± 3.2 and contrary to popular belief 28% of patients suffering from Graves' disease were overweight at presentation. 12 out of 18 male patient were smoker, however none of the female patients were smoker. Glycemic status was screened only in 30 patients (50%) at onset and 3 patients (10%) patients were found to be suffering from diabetes. Another 30% patients were suffering from either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The baseline characteristics are depicted in Table 1.

Table 1 — *Baseline characteristics of Study population*

Characteristics (n=60)	Values	Comments
Age at diagnosis	33.1 ± 10.1 years	4 paediatric patients
Sex (Female:Male)	42:18	
Duration of symptoms before presentation	7.7 ± 6.8 months	4 patients were suffering for more than 24 months
Goiter (Grade Ib or more)	55 (91.6%)	Only 27 (49%) complained neck swelling
Smoking	12 (20%)	All smokers are male
BMI (kg/m^2)	20.7 ± 3.2	28% overweight
Glycemic status at presentation (n=30)	10% diabetic 30% IFG or IGT	categorisation of dysglycemia could not be done
FT4 at presentation (n=46)	4.09 ± 1.89 ng/dl	

BMI-body mass index, IFG-impaired fasting glucose, IGT- impaired glucose tolerance, FT4- free thyroxine

Mode of presentation varied widely. Most common mode of presentation was tremor (93%), followed by palpitation (86.6%), weight loss (85%) and hyperdefecation (25%). Less than 50% patients complained of neck swelling among those having Goiter 1B or more. Thyroid brui was documented in 10% patients. Two patients presented with only eye symptoms. Overall 31 (51.6%) patients had eye signs and active eye disease was present in 5 (8.3%) patients. Dermopathy and acropachy were rare and was present only on clinical examination in 2 (3.3%) and 1 (1.6%) patients respectively. Table 2 summarises different modes of presentation. Diagnosis was mostly done by clinical examination (57% cases) such as presence of orbitopathy, dermopathy, acropachy, brui on thyroid gland auscultation. 23 patients (38%) needed help of isotope studies (99m Tc pertecnatate scan) which is the preferred modality in our institute. Use of TRAb for diagnosis was seldom used. Two patients with euthyroid graves orbitopathy and one pregnant patient was diagnosed as Graves' on basis of TRAb positivity. Table 3 summarises the use of different diagnostic modalities.

The preferred mode of therapy is medical. All patients were started with medical therapy (Carbimazole is the preferred drug). More than 90% patients achieved biochemical control within 3 month. 3 patients developed sore throat (but no neutropenia), 3 patient developed jaundice and 1 patient developed skin rashes. Those who developed jaundice and skin rash were started on lithium and sent for radioiodine ablation (RAI) therapy. All others were given choice between medical therapy and RAI therapy explaining all

Table 2 — *Presenting features of Graves' disease*

Clinical features	Comments
Features of thyrotoxicosis :	
Tremor (93%)	2 patients presented with only eye swelling
Palpitation (86.6%)	
Weight loss (85%)	
Neck swelling (45%)	
Brui (10%)	
Hyperdefecation (25%)	
Extrathyroidal manifestations :	
Orbitopathy 52%	CAS = 3/7 in 5 patients
Dermopathy 3.3%	
Acropachy 1.8%	

CAS = clinical activity score

Table 3 — *Use of different diagnostic modalities*

Modality	Percentage
Clinical	57%
Isotope studies	38%
Anti TSH-R antibody	5% (2 Euthyroid GO and 1 pregnant)

pros and cons. A total of 13 patients had chosen RAI therapy. Average dose required was 11.6 ± 2.9 mCi which rendered 8 patients hypothyroid, 3 patients euthyroid. 2 patients (15% of those undergoing RAI therapy) remained hyperthyroid despite 2 doses of RAI therapy, but required much less dose of carbimazole as compared to initial dose. Five patients underwent total thyroidectomy (2 patients had huge goiter, 2 patients had suspicious nodule and 1 patient had active eye disease with raised liver enzyme with carbimazole). Unfortunately 2 out 5 patients who underwent surgery developed permanent hypoparathyroidism. None of them developed vocal cord palsy. All the treatment modalities are summarised in Table 4. Among the 31 patients with orbitopathy, only 5 patients clinical activity score (CAS) = 3/7 and was treated with intravenous methylprednisolone as per our institutional protocol (Table 5). None of these patients required rituximab or orbital decompression for eye disease.

Table 5 — *Institutional protocol for Intravenous methylprednisolone for Graves' orbitopathy*

Clinical Activity score (CAS)	Mode of treatment
CAS 1 or 2	Conservative (Methycellulose eye drop, eye ointment if lagophthalmos, Dark glasses to wear, head end elevation)
CAS = 3/7	Checklist: Blood count, Plasma glucose, renal function, LFT, Chest X Ray Infusion Methyl prednisolone 500 mg IV for consecutive 3 days? repeat this dose monthly for 4 months (Cumulative dose 6g)

Discussion

Multiple literature worldwide have described the natural history, mode of presentation, diagnostic pitfalls and therapeutic options for graves' disease[2,6,7] but literature from India is scarce[8,9,10]. Boelaert K[11] *et al* reported weight loss, tremor and palpitations were presenting features in only 50-60% cases, whereas our study reports these symptoms to be present in 80-90% patients. Eye symptoms are also much higher in our cohort (51% *versus* 11%) as compared to that study. One of the main reason for these differences may be the age of patients as the study by Boelaert et al included only elderly individuals. Our cohort also reported a very high prevalence of goiter (91%) as compared to previous studies, possibly indicating delay in diagnosis and/or irregular treatment before presenting to us.High prevalence of dysglycemia at presentation is another interesting finding in our study. This is supported by previous literature where thyrotoxicosis per se was associated with glucose intolerance in approximately one-third of individuals, with frank diabetes occurring in a further 8% of patients[12]. Pre-existing diabetes mellitus may be aggravated or Graves' disease may be associated with type 1 diabetes as a part of polyglandular autoimmune syndrome. Also, excess thyroid hormone itself causes increased glucose production and expression of the hepatocyte glucose transporter 2 (GLUT-2) protein expression in liver[13] and there is some evidence for insulin resistance as the primary defect[12]. However despite these strong association, screening for diabetes was done only in 50% cases in our cohort.

In a survey done by Bartalena L[2], TRAb was an underutilised tool for diagnosis of graves' disease in 1991, but its use has gone up in 2011 due to its wide availability and being easy to perform. More than 50% doctors in North America and 70% in Europe now rely on TRAb for diagnosis of graves' disease. Our survey shows use of TRAb is bare minimal 11% and that's too for special cases only (Two patients with euthyroid graves' orbitopathy and one pregnant patient) (Fig 1). In that same survey by Bartalena L, it was found that RAI therapy was more popular in North America as first line treatment for graves but in Europe and Asia, medical therapy is the preferred one. Our survey results are keeping with them (Fig 2). In India, a report from 1993 indicated that antithyroid drugs were the preferred first-line treatment for Graves' disease[8], recently, in a tertiary referral centre in North India, 131I-radiotherapy has gained widespread acceptance[10]. Pradeep PV *et al*[9] from Uttarpradesh reported surgery for hyperthyroidism has negligible mortality and acceptable morbidity in experienced hands. Our survey reports high prevalence of surgical hypoparathyroidism among those undergoing surgery, may be this was due to selection bias as the cases were collected from an endocrine OPD. The advantage and disadvantages of medical, RAI therapy and surgery are summarised in Table 6.

Table 4 — *Mode of therapy used for Graves' disease*

Mode of therapy	Percentage	Side effects	Comments
Medical	70% 40 carbimazole 2 methimazole 0 PTU	5% sore thorat 5% liver dysfunction 1 skin rash	Mostly used
I^{131} ablation	21.6% (dose 11.6 ± 2.90 mCi)	61% hypothyroid	15% hyperthyroid (after 2 doses)
Surgery	8.3%	2 out of 5 developed permanent hypoparathyroidism	

Conclusion

A comprehensive overview of management of Graves' disease in Eastern India is described. Contrary to popular belief, a significant number of patients are overweight. There is high prevalence of dysglycemia at disease onset but often clinicians are

Table 6 — *Advantages and disadvantages of treatments for Graves disease (Adapted from Bartalena L2, permission not taken)*

Treatment	Advantages	Disadvantages
Antithyroid drugs	Conservative treatment No hospitalization required Low risk of subsequent hypothyroidism No radiation exposure No adverse effect on Graves ophthalmopathy Safe to use during pregnancy and breastfeeding	High relapse rate Requires frequent clinic visits for monitoring Poor adherence Adverse events (rarely major)
^{131}I-radiotherapy	Definitive treatment Low cost No hospitalization required No need for surgery or anaesthetic	Lifelong hypothyroidism Radiation exposure Slow control of hyperthyroidism Possible progression or *de novo* occurrence of Graves ophthalmopathy
Thyroidectomy	Definitive treatment No radiation exposure Prompt control of hyperthyroidism	Lifelong hypothyroidism Adverse events related to surgical procedure and anaesthetic Hospitalization High cost Permanent scar

reluctant to screen. Diagnosis is primarily made clinical examination, radioisotope studies done in doubtful cases. Requirement of usage of TRAb is still minimal and restricted to special cases only.Treatment is primarily medical therapy, which is reasonably safe. Radioiodine therapy is also a safe alternative, surgical therapy should be reserved for refractory cases.

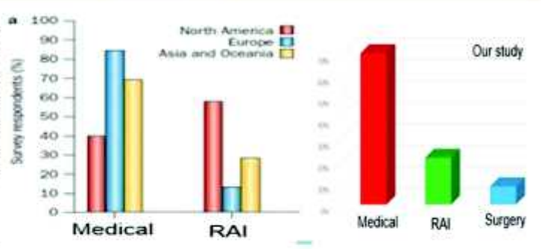

Fig 1 — Comparison of use of diagnostic tests for Graves' disease (Left side panel taken from Bartalena L2 and right side panel our data)

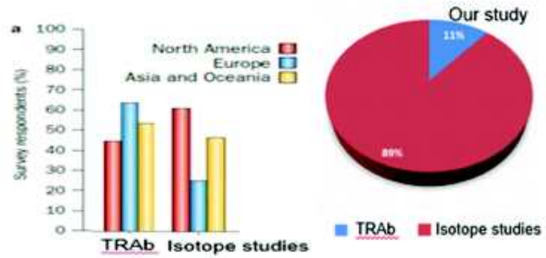

Fig 2 — Comparison of use therapeutic options for Graves' disease (Left side panel taken from Bartalena L 2 and right side panel our data)

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Review Article

Management of osteoporosis

Alpesh Goyal[1], Nikhil Tandon[2]

Osteoporosis is a major neglected public health problem associated with significant morbidity and mortality. Treatment in a patient with osteoporosis is targeted at reducing the future fracture risk, which is achieved through a combination of non-pharmacological and pharmacological interventions. Education on simple measures aimed at fall prevention, and adequate calcium and vitamin D supplementation should be ensured in all patients treated for osteoporosis. Medications approved for treatment of osteoporosis include antiresorptive agents (estrogen, calcitonin, selective estrogen receptor modulator raloxifene, bisphosphonates and denosumab) and anabolic agents (teriparatide and abaloparatide). A search for newer treatment targets has enabled development of two new effective drugs-odanacatib and romosozumab. However, these drugs have not been approved due to increased risk of stroke and cardiovascular events seen in the study participants. At present, combination therapy with anabolic and antiresorptive agents is not recommended due to lack of data on antifracture efficacy and cost-effectiveness. The sequential therapy should comprise of anabolic agent first, followed by an antiresorptive agent to maintain the bone mineral density (BMD) gains achieved with the initial treatment. BMD should be monitored periodically and increasing (or maintained) areal BMD without incident fractures indicates successful treatment.

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Key words **: Osteoporosis, postmenopausal osteoporosis, fractures, antiresorptive therapy, anabolic therapy.**

The treatment goal in a patient with osteoporosis is to reduce the risk of future fractures. This is accomplished through a combination of non-pharmacological and pharmacological interventions, which will be discussed in this chapter. There has been a great advance in the medical treatment of osteoporosis. While in 1980s, treatment options for postmenopausal osteoporosis (PMO) were limited to estrogen and calcitonin, in the current era, treatment armamentarium has expanded to include bisphosphonates, selective estrogen receptor modulator (raloxifene), monoclonal antibody to receptor activator of nuclear factor-ĸB (NF-ĸB) ligand (denosumab), parathyroid hormone analogue (teriparatide) and parathyroid hormone-related peptide analogue (abaloparatide). Insights from the rare sclerosing bone disorders and better molecular understanding of the bone cell biology has further enabled development of two new agents- cathepsin K inhibitor (odanacatib) and inhibitory monoclonal antibody to sclerostin (romosozumab).

Non-pharmacological Interventions :

It is important to emphasize following simple measures to reduce the fracture risk in each patient with osteoporosis[1].

(a) Fall prevention measures: Slippery floors, obstacles on the walking space and poorly lighted rooms may all increase the risk of falls and should be avoided. Patients should be instructed to use handrails while climbing stairs. Issues with vision, balance and proprioception may also increase the risk of falls and should be addressed appropriately.

(b) Weight bearing exercise should be encouraged, as much as possible, to improve muscle and bone mass. A sedentary lifestyle leads to low muscle mass, postural changes and deconditioning, increasing the risk of falls. In those with existing vertebral fracture, weight lifting and excessive strain on the spine while bending should be avoided.

(c) Avoid drugs that may increase the risk of falls (hypnotics, benzodiazepines, tricyclic antidepressants, alcohol) and predispose to osteoporosis (glucocorticoids, methotrexate, heparin, anticonvulsants). In patients with diabetes and/or hypertension, avoid hypoglycemia and/or hypotension to prevent falls.

(d) Ensure adequate calcium and vitamin D intake. Calcium and vitamin D deficiency may contribute to secondary hyperparathyroidism and the resultant bone loss in patients with osteoporosis. National Osteoporosis Foundation (NOF) recommends calcium intake (by diet and/or supplements) of 1000 mg/day for men aged 50-70 years and 1200 mg/day for women aged >50 years and men aged >70 years[2]. Calcium carbonate based calcium supplements are better absorbed when taken with food, while calcium citrate based supplements can be given regardless of the food timings.NOF also recommends vitamin D intake of 800-100 IU/day for adults >50 years of age[2].

Department of Endocrinology and Metabolism, AIIMs, New Delhi 110029
[1]MD, Senior Resident
[2]MD, Ph D, Professor & Head

Pharmacological Interventions :

Estrogen : In the era preceding the landmark Women's Health Initiative (WHI) study, estrogen used to be a popular therapy for prevention and treatment of PMO3.The Women's Health Initiative (WHI) study included >16000 postmenopausal women aged 50-79 years, who were randomised to conjugated equine estrogen (0.625 mg) plus medroxyprogesterone (2.5 mg) or placebo for a mean duration of 5.6 years. Though the risk of hip fracture and total fractures was significantly lower in the treatment arm, a concomitant increase in the risk of coronary heart disease, stroke and invasive breast cancer was seen[4,5]. The WHI results lead to a significant decline in the use of estrogen for PMO and currently it is used mainly as a short-term therapy to treat menopausal symptoms.

Calcitonin : Calcitonin (200 IU intranasal daily or 100 IU subcutaneous/intramuscular every other day) is Food and Drug Administration (FDA) approved therapy for treatment of PMO. However, due to modest anti-fracture efficacy compared to the other drugs and concerns regarding malignancy with long-term use, it has fallen out of favour in the current clinical practice[6,7].

Bisphosphonates : Bisphosphonates are the most commonly used drugs for prevention and treatment of PMO and glucocorticoid-induced osteoporosis. They are stable pyrophosphate analogs, which act through inhibition of the enzyme farnesyl pyrophosphate synthase. The enzyme is required for generation of isoprenoid lipids, which causes post-translational modification of guanine triphosphate (GTP)-binding proteins required for osteoclast viability and function[7]. While alendronate, risedronate and zoledronate have been shown to reduce the risk of both vertebral and hip fractures[8,9,10,11], the data for hip fracture reduction with ibandronate is lacking[12] (Table 1).

Hypocalcemia, vitamin D deficiency and renal dysfunction (glomerular filtration rate <30-35ml/minute) should be excluded before initiating treatment with bisphosphonates[13]. Oral bisphosphonates should be taken on empty stomach (reduced bioavailability with food) with a full glass of water and patients should be instructed not to lie down for 30-60 minutes after taking the medication (to prevent dyspepsia and esophagitis). Patients should also be warned about the possibility of developing fever and muscle aches within 24-48 hours after the intravenous zoledronate infusion (especially with the first dose). Rare side effects of bisphosphonate therapy include atypical femur fractures[14] (3-50 cases per 100,000 person-years) and osteonecrosis of jaw15 (1-10 cases per 100,000 person-years). It should be remembered that the benefit of treatment in a patient with high risk of fractures far outweighs the risk of these rare adverse effects[16] (approximately 80-5000 fragility fractures are prevented for 1 atypical fracture fracture associated with bisphosphonate treatment).

Selective Estrogen Receptor Modulators (SERMs) : SERMs have estrogen agonistic action at bone and antagonistic action at breast and uterus. Raloxifene is the prototypical SERM which is approved for prevention and treatment of PMO. It has been shown to reduce the risk of vertebral fractures, but the data for hip fractures is lacking[17] (Table 1). The adverse effects associated with raloxifene use include hot flashes and increased risk of venous thromboembolism. Bazedoxifene is another SERM, which in combination with conjugated estrogen has been shown to reduce hot flashes and has been approved by FDA for prevention of hot flashes and osteoporosis in postmenopausal women.

Denosumab : Denosumab is a fully human monoclonal antibody to receptor activator of NF-ĸB ligand (RANKL). RANKL along with macrophage colony-stimulating factor (M-CSF) is required for osteoclast development; denosumab, thus, works as an antiresorptive agent. In the FREEDOM trial18, denosumab was found to reduce the risk for both vertebral and hip fractures (Table 1). Like bisphosphonates, hypocalcemia and vitamin D deficiency should be excluded before starting treatment; however, renal dysfunction (of any severity) is not a contraindication to denosumab use. Rare adverse effects of denosumab include atypical femur fractures and osteonecrosis of jaw. Cost is often a limiting factor with denosumab therapy.

Teriparatide : Teriparatide (parathyroid hormone 1-34) is a parathyroid hormone (PTH) analogue which is FDA approved for the treatment of PMO. Its use as an agent to treat osteoporosis is based on the observation that, while continuous PTH exposure leads toincreased bone resorption, intermittent PTH exposure results in increased bone formation as well as bone resorption, with a net anabolic effect. The data on vertebral fracture reduction with teriparatide is impressive, however, hip fracture data is lacking[19] (Table 1). Due to the increased risk of osteosarcoma in rodents treated with high dose of teriparatide, a "black box" warning has been added by FDA and the treatment duration limited to 24 months. Contraindications to the use of teriparatide include hypercalcemia, hyperparathyroidism, Paget's disease of bone, history of bone irradiation, open epiphysis, unexplained elevation in alkaline phosphatase (ALP) of bone origin and severe renal dysfunction.The cost of therapy and compliance with daily injection are the factors commonly limiting use of teriparatide therapy.

Table 1 — *FDA approved drugs for the treatment of postmenopausal osteoporosis*

Drug (Pivotal study)	Dose	VF (% Risk reduction)	HF (% Risk reduction)	NVF (% Risk reduction)	Reference
Alendronate (Fit)	70 mg/week p.o. 10 mg/day p.o.	48%	53%	36%	8
Risedronate (Vert and Hip)	35 mg/week p.o. 5 mg/day p.o.	41%	40%	39%	9,10
Ibandronate (Bone)	150 mg/month p.o. 2.5 mg/day p.o.	50%	N/A	No. Significant reduction only in subgroup analysis	11
Zoledronate (Horizon)	5 mg/year i.v.	70%	40%	25%	12
Raloxifene (More)	60 mg/day p.o	30%	N/A	No	17
Denosumab (Freedom)	60 mg/6 months s.c.	68%	40%	20%	18
Teriparatide (Neer et al)	20 ug/day s.c. for 2 years	65%	N/A	53%	19
Abaloparatide (Active)	80 ug/day s.c for 2 years	86%	N/A	43%	21

FDA-food and drug administration, VF-vertebral fracture, HF-hip fracture, NVF-nonvertebral fracture, p.o.-per oral, i.v.-intravenous, s.c.- subcutaneous, N/A-data not available.

Abaloparatide : Abaloparatide (parathyroid hormone-related peptide 1-34) is a parathyroid hormone-related peptide (PTHrP) analogue which is the latest addition to the list of FDA approved agents for the treatment of PMO. Although both teriparatide and abaloparatide act at PTH receptor type 1, teriparatide activates receptor towards R0configuration (resulting in persistent intracellular cyclic adenosine monophosphate (cAMP) release), while abaloparatide activates receptor towards RG configuration (resulting in more transient cAMP release)[7]. The net resultwith abaloparatideis stimulation of bone formation, with less concomitant bone resorption, increasing the anabolic effect and decreasing the risk of hypercalcemia, compared to teriparatide[20]. Abaloparatide has been shown to have increased bone mineral density (BMD) response at spine compared to teriparatide and a highly positive response at hip, where teriparatide has been shown to have only marginal effects. In the ACTIVE trial, incidence of hypercalcemia was found to be lower with abaloparatide (3.4%) than teriparatide (6.4%)[21].The risks, warnings and contraindications with abaloparatideare similar to teriparatide.

CathepsinK inhibitor : CathepsinK is an enzyme secreted by mature osteoclasts to degrade bone matrix proteins. Loss of function mutation in the gene encoding for cathepsinK results in a rare sclerosing bone disorder "pyknodysostosis", characterised by decreased osteoclast resorptive activity with preserved osteoblast function. In the LOFT trial[22], cathepsinK inhibitor odanacatib (50 mg/day) was compared with placebo in >16,000 women with PMO and was found to significantly reduce the risk of vertebral, nonvertebral and hip fractures. However, due to the increased risk of stroke (HR 1.16, 95% CI 1.10-1.71), Merck & Co, in 2016, decided to discontinue the development of this agent.

Sclerostin inhibitor : Sclerostin is an endogenous negative regulator of Wnt signaling pathway, which results in decreased osteoblast function and bone formation. Absence of functional sclerostin results in the clinical phenotype of two rare genetic disorders "sclerosteosis" and "van Buchem's disease", both characterised by increased bone mass. Romosozumab is a humanized monoclonal antibody to sclerostin, which has been shown to reduce the risk of vertebral fractures in women with PMO. In the phase 3 FRAME trial[23], romosozumab at a dose of 210 mg subcutaneous once/month was compared with placebo in >7000 women with PMO and was shown to significantly reduce the risk of vertebral fractures by 73% at 12 months. Adverse effects include injection site reaction, atypical femur fracture, osteonecrosis of jaw and increased risk of cardiovascular (CV) events. Owing to the increased risk of CV events, FDA in 2017, rejected the approval of romosozumab for PMO, till more safety data is available from other studies.

Role of combination and sequential therapy : There is no rationale in combining two antiresorptive agents together. Combination of anabolic agent (teriparatide) with antiresorptive agents (zoledronate, denosumab) has been studied in two separate clinical trials[24,25]. The combination therapy was found to be associated with greater BMD increase at the hip and spine than either drug alone; however, antifracture benefit of this strategy remains to be seen. Thus, combination therapy cannot be recommended currently, till more data on antifracture efficacy and cost-effectiveness becomes available.

When using teriparatide and bisphosphonate in a sequential therapy, teriparatide should preferably be used first followed by bisphosphonate. This is explained by the fact that most important anabolic effect of teriparatidetherapy is achieved during the initial few months of therapy and its use after bisphosphonate therapy has been associated with delayed and blunted anabolic effect, as shown by the response in bone formation markers and BMD[26].

Drug holiday : In the 5 year extension trial of alendronate (FLEX)27 and 3 year extension trial of zoledronate (HORIZON extension trial)28, patients were randomised to receive continued bisphosphonate therapy or placebo. In both the studies, there was small but significant decline in BMD at hip and spine in subjects who discontinued therapy at 3 or 5 years, however, even at the end of follow-up, the BMD remained above pre-treatment level, suggestive of residual antiresorptiveeffect of these agents on the bone. The risk of clinical vertebral fractures and morphometric vertebral fractures was increased in the placebo group in alendronate and zoledronate extension trials respectively. Based on the results of these two studies, bisphosphonates drug holiday should only be tried in patients with low risk of fractures; patients at high risk of fractures (prevalent vertebral fractures, history of fragility fractures or low femoral neck BMD at attempted discontinuation (T score =-2.5)) should continue to receive treatment. During the drug holiday, patient should be followed closely (BMD at 6-12 months interval) and treatment re-initiation considered in case of significant decline in BMD, increase in bone turnover markers (BTMs) and development of new osteoporotic fractures. It is important to note that the residual effect has only been conclusively demonstrated with alendronate and zoledronate. While limited data with risedronate suggests rapid offset and lesser residual effect[29], the long term data with ibandronate is not available. The residual effect seen with the two bisphosphonates also contrasts with other agents (such as estrogen, raloxifene, denosumab and teriparatide), where BMD gains are rapidly lost after 1-2 years of the treatment discontinuation and BTMs quickly return to pre-treatment levels[30,31,32].

Indications for treatment : According to NOF2, postmenopausal women and men above the age of 50 years with following should be considered for treatment:

(a) Hip or vertebral (clinical or morphometric) fracture

(b) T score $\leq$-2.5 at the femoral neck, total hip or lumbar spine by dual-energy x-ray absorptiometry (DXA)

(c) Low bone mass (T score between -1 and -2.5 at the femoral neck, total hip or lumbar spine by DXA) and 10 year probability of hip fracture $\geq$ 3% or 10 year probability of major osteoporotic fracture $\geq$ 20% by fracture risk assessment tool (FRAX)

Monitoring osteoporosis treatment : Serial BMD measurements (done at interval of 1-2 years) are most commonly used to monitor osteoporosis treatment. However, whether the long term antifracture efficacy of the treatment is governed by increased (or maintained) BMDremains a subject of debate[33]. Serial BMD measurement should be done on the same DXA machine and areal BMD (gm/cm^2) change should be taken into account. A stable or increasing BMD (BMD increase more than the least significant count) without incident fractures suggests successful treatment. Adequate calcium and vitamin D supplementation should be ensured and biochemistry (serum total calcium, inorganic phosphorous, alkaline phosphatase, albumin, creatinine, PTH, 25(OH)D and 24 hour urine calcium/creatinine) should be repeated at 6-12 months interval.

Conclusion :

Management of osteoporosis involves both non-pharmacological and pharmacological interventions directed towards reduction of the future fracture risk. With better understanding of the bone biology, newer molecular targets are being explored, diversifying the available treatment options. Better awareness among the physicians may improve the wide treatment gap associated with this commonly neglected public health problem.

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Review Article

Vitamin D deficiency in India

Mohammad Shafi Kuchay[1], Ambrish Mithal[2]

Vitamin D deficiency is prevalent in India across all age groups and geographical regions. Several factors are responsible for this widespread deficiency of vitamin D such as sun-avoiding behavior, atmospheric pollution, lack of vitamin D in common food items consumed in India and so on. Clinical features of vitamin D deficiency depends upon the age of the person. In the growing age, vitamin D deficiency causes rickets that manifest as growth plate abnormalities. In adults, vitamin D deficiency leads to osteomalacia that manifest as easy to break bones. Mild to moderate vitamin D deficiency in adults leads to bone loss, probably secondary to elevated parathyroid hormone. Vitamin D insufficiency has also been associated with a number of chronic inflammatory and neoplastic disorders. However, the causal role of vitamin D insufficiency in these disorders is yet to be proved. Several doses and regimens have been used for preventing and treating vitamin D deficiency. Overzealous correction of vitamin D deficiency has also lead to the increased incidence of vitamin D toxicity. In this article, we will discuss the overview of burden of vitamin D deficiency in India, its clinical presentations as well as some suggestions for treating vitamin D deficiency.

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***Key words* : Vitamin D deficiency, Rickets, Osteomalacia, Osteoporosis, 25(OH)D, vitamin D toxicity**

- **Vitamin D is an essential factor for optimal bone health and may impact other medical disorders unrelated to bone and mineral metabolism.**
- **A serum A serum 25(OH)D level of 12.5 ng/mL is sufficient for prevention of rickets and osteomalacia.**
- **For general population, 25(OH)D values of 20 ng/mL may be considered adequate. There is no evidence to support that levels above 40 ng/mL provide any additional benefit.Therefore, 25(OH)D levels between 20-40 ng/mL are optimum for most of the population.**
- **The optimum serum 25(OH)D level for patients with bone disorders like osteoporosis is 30 ng/mL.**
- **Overzealous correction of vitamin D deficiency, especially with parenteral mega-doses of vitamin D preparations, should be avoided.**

(1) What is the Burden of Vitamin D Deficiency in India?

Hypovitaminosis D has been reported from India across all ages: pregnant women, newborns, children and adolescents, young adults, and older men and women. A review of the global vitamin D status by the International Osteoporosis foundation in 2009 underscores the fact that South Asia may be one of the worst affected regions in the world[1]. Vitamin D deficiency disorders such as rickets in children and osteomalacia in adults continue to exist in the Indian population[2].

Several factors have been proposed to explain the high prevalence of vitamin D in Indians. These include the following :

(1) Poor sun exposure, especially in urban Indians — Culturally, Indians avoid the sun for fear of skin darkening orbecause the summer sun delivers discomforting heat. This sun fleeing behavior contrasts with the sun seeking behavior of Europeans and North Americans, where, because of the otherwise cold environment, the sun's warmth is generally considered welcome

(2) Clothing habits — Traditionally, Indians, even when in the sun, tend to keep their bodies well covered.

(3) Skin pigmentation — Melanin in the skin competes with 7-dehydrocholesterol for UVB rays. Greater amounts of melanin in the skin reduce the efficacy of vitamin D synthesis. Pigmented skin requires a longer duration of sun exposure to synthesize equivalent amount of vitamin D as compared to a Caucasian skin. There are six types of skin based on degree of pigmentation and propensity to burn or tan. The lightest north European skin is classified as type 1 and African skin as category VI. Indians belong to skin category IV and V.

(4) Atmospheric pollution — It may be playing a role in reducing the efficiency of vitamin D photosynthesis in Indian cities. The short UVB wavelengths are scattered by this process. There is a report of high incidence of vitamin D deficiency rickets in toddlers living in areas of high atmospheric pollution in Delhi, India.

(5) Food habits and lack of fortification — effectively, there is negligible vitamin D available from dietary sources in India. Compounding this is the absence of vitamin D

Division of Endocrinology and Diabetes, Medanta The Medicity, Sector 38, Gurugram 122001
[1]MD, DM, Consultant and Corresponding author
[2]MD, DM, Chairman

fortification andlow dietary calcium intake in India which further aggravates the problem.

Vitamin D status in young adults : Numerous reports, from across India haveshown a high prevalence of hypovitaminosis D, ranging from 70% to 98% in adult Indians. In a series of studies from North India-from Delhi, Lucknow, Srinagar and other cities-vitamin D deficiency has been shown to be very common[3-7]. Winter levels of circulating 25(OH)D have been shown to be as low as 4-5 ng/mL in Delhi and Lucknow. Data from across India, including the South-Tirupati, Vellore and surrounding areas, and West- Mumbai- is similar, although the levels seem to be slightly better in the South than in the North, probably reflecting the difference in latitude[8-10].

Vitamin D status in older adults and elderly : Older adults and elderly are particularly at risk for developing vitamin D deficiency as the efficiency of synthesis of vitamin D in skin declines with advanced age. A study from Delhi found that 91.3 % urban adults (aged 50-65 years) had vitamin D deficiency with mean 25(OH)D levels of 9.7 ng/mL[11-15]. Similar proportion of subjects (91.2 %) in the age group of 65 years and above had mean serum 25(OH)D levels of 9.9 ng/mL. Other studies have shown similar findings[16-17]. In a study from India, outdoor workers with prolonged sun-exposure were vitamin D-sufficient, with higher serum 25(OH)D (29.0 ng/mL) than the indoor workers (10.9 ng/mL) during summer[18].

Vitamin D status in children : Approximately 40-50% of total skeletal mass is accumulated during childhood and adolescence. Severe vitamin D deficiency, usually associated with 25(OH)D levels < 5.0 ng/mL, results in rickets and osteomalacia. However, these clinically overt cases of vitamin D deficiency would represent only the tip of the iceberg. The mean serum concentrations of 25(OH)D reported in children and adolescents from Delhi were 11.8 ± 7.2 ng/mL and 13.8 ± 6.9 mg/mL respectively, which are much lower than the recommended level of 20 ng/ml. Overall more than 85% of school children, both from government and private schools, had suboptimal levels of 25(OH)D.Studies from other parts of India (eg, Pune) show similar results[19-22].

Vitamin D status in pregnancy, neonates and infants : Data on vitamin D status in pregnant and lactating women from Delhi, Lucknow and Mumbai reveal a very high prevalence of hypovitaminosis D (84-93%). One study suggested that vitamin D supplementation with vitamin D during pregnancy could result in better anthropometric indices the newborns up to nine months of follow up. Studies from India have shown significant correlation of serum 25(OH)D concentration between mother-infant pairs. Low vitamin D levels in mothers result in low vitamin D levels in cord blood and newborns. Exclusively breastfed infants continue to have low 25(OH)D levels[23-27]. One study suggested that the risk of infants suffering from moderate to severe vitamin D deficiency was three to four times greater if their mothers had levels below 10 ng/mL. It has also been shown that infants of mothers with hypovitaminosis D are at higher risk of hypocalcemic seizures. A recent study reevaluated the effect of weekly vitamin D supplementation up to six months, on mortality, morbidity and growth of low birth weight full term infants. It observed that vitamin D supplementation resulted in significant increase in SD scores for weight, length and arm circumference and decreased proportion of children with stunted growth[28-30].

Data from Rural populations:In a study from rural India (Agota village, about 80 kilometers from Delhi), vitamin D deficiency was found in 68.5 % of adults and the mean serum 25(OH)D levels were 14.5 ng/mL.In another study, rural postmenopausal women near Tirupatiwere found to have mean serum 25(OH)D levels of 14.6 ng/mL- 82 percent of them were deficient.Data from rural areas in the vicinity of Lucknow,(Uttar Pradesh) as well from Tamil Nadu confirms the widespread nature vitamin D deficiency in rural India[31-34].

Thus, there is high prevalence of vitamin D deficiency across all age groups, social strata and geographical regions in the Indian population.

(2) What are the Optimum Circulatory 25(OH)D Levels for Bone Health?

There is lack of unanimity in international guidelines on this issue. A serum 25(OH)D level of 12.5 ng/mL is sufficient for prevention of rickets and osteomalacia. For general population, 25(OH)D values of 20 ng/mL may be considered adequate. There is no evidence to support that levels above 40 ng/mL provide any additional benefit.Therefore, 25(OH)D levels between 20-40 ng/mL are optimum for most of the population. The optimum serum 25(OH)D level for patients with bone disorders like osteoporosis is 30 ng/mL.It must be noted that many Indians may require supplementation to achieve this level[35-36].

(3) What is the Clinical Presentation of Vitamin D Deficiency ?

Most people with low vitamin D levels do not have any symptoms, and the adverse impact of the deficiency is on bone health in the long term. Severe vitamin D deficiency, particularly when coupled with low calcium intake gives rise to numerous clinical symptoms, traditionally described, and enumerated in Tables 1 and 2.

(4) What are the Indications for Vitamin D Testing ?

There is a consensus among expert groups that universal screening for vitamin D status is not recommended. Persons who should be tested for Vitamin D status include:

- Those with symptoms and/or signs suggestive of vitamin D deficiency, for example suspicion of osteomalacia, osteoporosis or musculoskeletal symptoms
- Those at high risk of vitamin D deficiency such as inflammatory bowel disease, bariatric surgery, those on drugs like antiepileptics, antitubercular medication, glucocorticoids, antiretroviral drugs and ketoconazole, those with chronic kidney or liver disease.
- In a resource constrained environment recommended doses may be used without estimating levels even in these situations after ruling out hypercalcemia.

(5) How do we Treat Vitamin D Deficiency?

Cholecalciferol is the only preparation available in India. Available preparations and strengths include drops containing 400 IU/mL and 800 IU/mL, capsules containing 1000 and 2000 IU /capsule, syrup/sachets/softgel capsules containing 60,000 IU and injections containing 300,000 and 600, 000 IU. In addition, calcium preparations also contain variable amounts of vitamin D (100-1000 IU/tablet)

The active form of vitamin D (calcitriol) should not be used in routine treatment of vitamin D deficiency. Its use should be limited to hypocalcemic emergencies and resistant forms of rickets (hypophosphatemic and vitamin D dependent rickets), or in patients with kidney disease.

Treatment option 1: Weekly doses followed by maintenance. In 60,000 IU of vitamin D3, once a week for 8 Weeks, followed by maintenance therapy of 1500–2000 IU/Day or 60000 IU once a month.

This option is for patients with metabolic bone disease (rickets/Osteomalacia) along with calcium supplementation. This regimen can also be used sometimes in asymptomatic individuals if levels are very low (25OHD<10 ng/ml).

Treatment Option 2: 60,000 IU to 120,000 IU per Month. This option is for apparently healthy subjects with vitamin D deficiency can be given monthly doses of 60,000 in summer and 120,000 in winter.

Treatment Option 3: Daily Supplementation of 1000-2000 IU. This option is typically used in those who need of simultaneous calcium with vitamin D (elderly, low intake of calcium) and have mild deficiency/borderline 25 (OH)D levels. Can also be used for prevention /maintenance therapy with or without calcium.

Treatment Option 4: Parenteral mega doses 0f 300,000 to 600,000 IU. Intramuscular vitamin D can be used if there are issues with absorption of oral vitamin D-not more frequently than once in 6 months. It can also be used occasionally in cases where compliance is a challenge. Parenteral vitamin D should not be the first-line recommendation primarily due to significant inter-individual variability in absorption and risk of misuse/overdose leading to severe hypercalcemia.

Duration of therapy : Once the treatment phase is over, long term- maybe lifelong- maintenance is probably required, in the doses outlined in options 2 and 3. The levels of 25(OH)D tend to fall to baseline values over a period of few weeks to months if supplementation is discontinued.

(6) What Causes Vitamin D Toxicity ?

Improper use of pharmaceutical preparations of vi-

Table 1 — *Clinical presentation of vitamin D deficiency in adulthood*

Symptoms :
- Isolated or generalized aches and pains in bones and muscles
- Muscle weakness
- Difficulty in squatting standing, walking
- More frequent falls

Signs :
- Waddling gait/Proximal muscle weakness
- Anteriortibial tenderness
- Rib cage tenderness
- presentation with fractures

Table 2 — *Clinical features of rickets*

Symptoms and Signs Due To Deformities

Skull :
- o Frontoparietal bossing
- o Wide open anterior fontanelle (AF), delayed closure of AF
- o Craniotabes- Ping pong ball sensation of skull bones- best felt on occiput and parietal bones away from the sutural lines.

Chest :
- o Rachitic rosary- beading of costo-chondral junction, best examined by palpation along the long axis of the rib
- o Harrison's groove- along the lower thoracic cage corresponding to costal attachments of diaphragm.

Limbs :
- o Wrist widening
- o Genuvalgum(knockknees), genuvarum (bowlegs)
- o Windswept deformity- combination of varus deformity of one leg and valgus deformity of the other
- o Ankle widening, double malleolus – secondary to grooving of tibia by the tendon of tibialisanterior
- o Pelvic deformities, coxavara

Spine :
- o Kyphoscoliosis- seen in longer and more severe deficiency

Symptoms Due To Hypocalcaemia (more common in young infants)
- o Apnoea
- o Seizures
- o Tetany
- o Irritability
- o Stridor, wheezing
- o Dilated cardiomyopathy

Other Features :
- o Hypotonia- proximal weakness, delay in gross motor milestones, protuberant abdomen, visceroptosis
- o Delayed dentition, enamel hypoplasia, dental caries
- o Bone pains
- o Repeated infections due to impaired phagocytosis, repeated chest infections due to ciliary dysfunction, respiratory muscle weakness, compliant chest

tamin D is the most common cause of vitamin D toxicity[37-39]. The Food and Nutrition Board recommends the tolerable upper intake level (UL) as 1000 IU daily for infants 0-6 months of age, 1500 IU daily for infants 6-12 months of age, 2500 IU daily for children 1-3 years of age, 3000 IU daily for children 4-8 years of age, and 4000 IU daily subsequently throughout life. The IOM has concluded that vitamin D below 10,000 IU/day is not usually associated with toxicity. Most of the reports of vitamin D toxicity have documented vitamin D intake of >40,000 IU/day. Hypercalcemia and vitamin D toxicity were noted in children when they received total dose of 240,000-4,500,000 IU of vitamin D.

Presentation of vitamin D toxicity usually depends on the serum calcium level. Patients with mild or moderate hypercalcemia are usually asymptomatic. The usual symptoms are anorexia, nausea, weight loss, constipation, rarely acute pancreatitis, polyuria/polydipsia, dehydration, confusion or coma. Vitamin D toxicity should be strongly suspected clinically in patients who are being treated with pharmacological dosages of vitamin D. It can be life threatening if not treated promptly. The characteristic laboratory findings of vitamin D intoxication are high serum and urinary calcium level, normal or high serum phosphate level, low parathormone and high vitamin D levels. The final diagnosis of vitamin D intoxication is made by determining the serum 25(OH)D level.Risk factors for vitamin D toxicity include extremes of ages, concurrent use of thiazide, impaired renal function and coexisting disorders such as sarcoidosis and tuberculosis.

People with asymptomatic vitamin D deficiency can be managed with maintenance dose with negligible risk of vitamin D toxicity.Parenteral preparations of vitamin D should be used only in cases with documented evidence of malabsorption.

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Review Article

Consensus recommendations for the management of peripheral neuropathy in India

A V Srinivasan[1], S Paranjothi[2], Kalyan B Bhattacharyya[3], Debasish Maji[4], Daya Kishore Hazra[5], Pradeep Talwalkar[6], Sanjiv Shah[7], Rakesh Kumar Sahay[8], Deepak Khandelwal[9]

Peripheral neuropathy (PN) poses a high disease burden in India as compared to developed countries, owing to higher prevalence of diabetes cases, nutritional deficiencies, infectious diseases, and exposure to toxins. There are currently no Indian clinical guidelines in place for the management of this neurological condition. Hence, there exists a need to develop standard guidelines for management of PN specific to the Indian population considering international guidelines may not be fully applicable to this patient population. To better understand the causes and management of PN in India and develop a multi-disciplinary expert consensus statement providing guidance to primary care physicians for the diagnosis and treatment of PN in India. In November 2017, a meeting of experts in the field of neuropathy, including neurologists, diabetologists, and endocrinologists was conducted in Chennai, India. The expert committee discussed underlying causes, current clinical practice(s) for diagnosis, treatment guidelines and alternative treatment options for PN in India. The group of experts arrived at consensus-based recommendations for (a) simple steps for diagnosis and (b) treatment as per the guidelines and treatment options used in clinical practice in India. Recommendations based on consensus on PN management in India were developed. The experts developed a simple, four-step, clinical diagnostic checklist as a guidance tool to help improve the diagnosis and identification of the cause of PN by primary care physicians. For treatment, the experts recommended that in addition to symptom management, treatment of underlying cause and restoration of nerve health is a vital step in PN management. The importance of alternative treatment options such as neurotropic B vitamins and alpha-lipoic acid, in the treatment of PN and nerve health restoration was highlighted. The expert group also discussed prophylactic, therapeutic and maintenance treatment options in different patient settings. This consensus statement is aimed at providing useful clinical guidance to primary care physicians on PN diagnosis, treatment and management. Nonetheless, there is a need for further experience-based cross-speciality deliberations to formulate holistic guidelines for the management and treatment of PN in India. [*J Indian Med Assoc* 2018; **116:** 45-55]

Key words **: Peripheral neuropathy, neuropathic pain, vitamin B12, alpha-lipoic acid, neurotropic B vitamins**

Peripheral neuropathy (PN) is a commonly encountered disorder of the nervous system in the Indian population. The disease process can start from systematic illnesses, toxins etc and leads to impairment and damage of nerves[1]. Its association with a myriad of aetiological factors makes it a diagnostic and therapeutic challenge to treating physicians, especially for those in primary care. While diabetes is recognised as the most common cause of PN, alcohol misuse, infectious diseases, deficiencies of neurotropic vitamins, toxins and many other causes, are documented to cause PN with varying prevalence numbers. Additionally, a significant number of patients suffer from PN without any identifiable cause (idiopathic neuropathy) which further complicates effective management for the treating physician[2,3]. A further barrier is the poor documentation of the disease and its respective causeleading to a lack of information on the high risk populations and possibly suffering patients.

In the Indian subcontinent, diabetes is still the most common cause of PN. However, contrary to the global picture, where diabetes remains the leading cause, in India other causes are also highly prevalent, albeit not very well documented. In view of the wide-spectrum of agents/

[1]MD, DM, Emeritus Professor, The Tamilnadu Dr MGR Medical University, Chennai 600032
[2]MD, DM, Senior Consultant in Neurology, Institute of Neurosciences, Pondicherry 605013
[3]MD, DM, Head, Department of Neuromedicine RG Kar Medical College, Kolkata 700004
[4]MD, DM, Professor and HOD, Vivekananda Institute of Medical Sciences, Kolkata 700026
[5]MD, MSc Chief Consultant, Boston Medical Centre, Agra 282005
[6]MD, Consultant Diabetologist,Shushrusha Hospital, Mumbai 400083
[7]MBBS, MD, Endocrinologist,Nanavati Super-Speciality Hospital, Mumbai 400056
[8]MD, DM,Professor and Head, Department of Endocrinology, Osmania Medical College & Hospital, Hyderabad 500095
[9]MD, DM, Senior Consultant, Endocrinology and Diabetes, Maharaja Agrasen Hospital, Delhi 110026

factors involved in the aetiology of PN, primary care physicians (PCPs) as well as specialists like neurologists, dermatologists, endocrinologists, orthopaedics etc. play an important role in the management of PN[4,5].

In order to better understand the causes and management of PN in India and to develop a multi-disciplinary expert consensus statement providing guidance to PCPs for the diagnosis and treatment of PN in India, a group of experts including neurologists, diabetologists, and endocrinologists, formed a consensus panel and met in November 2017 in Chennai.

Although therapeutic advancement in treatment of PN is rapidly progressing, due to the insidious nature of this disease and lack of protocol/guidelines/consensus among physicians, treatment can be frustrating for both physicians and patients alike.

In India, the scientific literature on PN,to which physicians can refer for best practice, is inconsistent with regards to aetiological, diagnostic, and evidence-based recommendations[1,6-9].

This paper summarises outcomes of the discussions undertaken by the aforementioned experts along with their recommendations for best clinical practices as a guidance for PCPs and physicians from different specialties.

Epidemiology of Peripheral Neuropathy in India :

Underestimated Burden of PN and its Clinical Relevance

PN is generally associated with symptoms of numbness, stabbing pain, tingling and burning sensation with deranged neural conduction, often affecting nerves in the extremities but also other parts of peripheral nerves. Prevalence of PN varies as a function of casual factors including the prevalence of underlying disease specifically associated with PN and environmental risk factors. Globally, different sources report different prevalence levels due to non-uniformity in case definition and case ascertainment[10,11]. Studies in different countries also report adopting the World Health Organization (WHO) protocol for diagnosis of PN which revealed variable prevalence across countries, ranging from 0.8 to 32.5 per 1,000 population[1,12,13-15].

The epidemiological picture of PN in India is somewhat different from the global context. The expert panel speculated, this may be due to presence of multiple ethnicity, culture, varied environmental factors etc. Community based studies in India show a prevalence that ranges from 0.5 (0.05%) to as high as 240 per 1,000 (24%) population[1]. The older population is affected more (30-40%) as compared to younger population (2-8%), as a result of higher prevalence of other diseases, medication intake, and other cumulating factors which are associated with the ageing process[1,16]. Geographically, significant variation in prevalence has been reported between different regions and also in urban versus rural areas[1]. While this may be attributed by location specific environmental factors, lack of clinical documentation could be another important factor leading to this observation.

The expert group at the consensus meeting expressed their concern that in India, PN is likely to be significantly under-diagnosed and hence, the burden of disease underestimated. They acknowledged thatthere is a lack of sufficient data available to understand epidemiology of PN in India creating a burden for PCPs not having a clear picture on the patients they have to identify. Negligence of mild and nagging symptoms of PN by physicians or lack of awareness on the 'at risk' population were identified as major causes for under-diagnosis of PN in India.

Aetiology of PN is Different in the Indian Context

Epidemiology of PN suggests involvement of a number of causative agents or pathological processes. The expert panel agreed that identifying the most common causes of PN is the first key step for PCPstowards improving the diagnosis of PN. Many studies outside India suggest that the most common cause of neuropathy as well as polyneuropathy is diabetes (34.8%), followed by alcoholic neuropathy (11.1%). The aetiology remains unknown inapproximately 22% of cases[17].

In the opinion of the experts, diabetes is the most common cause of PN in India as well. However, while prevalence of PN in diabetic patients was more than 50% in western countries[18], literature reports a prevalence of 10 to 32% in India[1]. A range is reported as different outcomes are documented in different sources, which might reflect the heterogeneity of the population across India. Whether the number differs from the globally reported prevalence due to a higher number of undiagnosed and unreported PN cases remains unknown.The experts highlighted that the documentation is not consistent and not appropriate. In their opinion diabetic patients have a higher prevalence of neuropathy than those in developed countries due to greater prevalence of concomitant causes. Furthermore, experts anticipate the incidence of PN to rise in India, as a result of increasing number of diabetic patients from 73 million in 2017 to 134 million expected in 2045[19].

Experts further highlighted that in India, unlike in western countries, infectious diseases are still highly prevalent and are one of the common causes of PN.As per available literature, inflammatory disorders like GuillainBarre Syndrome (GBS), and infectious diseases, primarily HIV and leprosy, have been found most commonly associated with PN[1]. Certain anti-retroviral drugs can also induce neuropathy[20,21]. India alone contributes to more than 55% of the global burden of leprosy, which is primarily a disease of peripheral nerves,thus making it a common cause of PN in this country[22]. Also common, and more prevalent than in developed countries, is post-herpetic neuralgia, due to the lowervaccination rate[23].

Alcoholic abuse and environmental exposure to toxic agents like arsenic, lead, mercury and organophosphates are significant contributors to incidence of PN in India[1].

Another major cause of neuropathyis deficiency of neurotropic vitamins due to different reasons such as malabsorption and dietary restrictions[24]. In 29-40%[25-27] of the Indian population adheres to a strict vegetarian diet which leads to nutritional deficiencies, particularly vitamin B12 (cobalamin), thus affecting nerve health. Prolonged exposure to certain drugs can also deplete the B vitamin reserves in the body, leading to drug-induced deficiencies. Particularly in India, high prevalence of diseases like diabetes, tuberculosis and hypertension sees rampant use of B vitamin depleting drugs like metformin, isoniazid/cycloserine and loop diuretics, respectively[28-31]. An indicative list of causes of PN is provided in Table 1[1,17-35].

Recommendations for Diagnosis :

Preliminary Investigation of Patients Suffering from PN is Essential

The experts, during the consensus meeting, acknowledged that an effective treatment of PN starts with an accurate and timely diagnosis combined with appropriate and prompt management. This necessitates the need for effective communication between physicians and their patients to drive better treatment outcomes. As such, awareness among physicians about the benefits of timely diagnosis and treatment was agreed to be of considerable value. According to a study, the median duration of symptoms was found to be 5.9 months prior to its presentation[36]. The experts estimated that the average time taken by PN patientsto get diagnosed is 5 years or more. It was acknowledged that diagnosis is a burden for majority of physicians due to limited time and availability of tools in primary care setting. According to estimation of the experts, 95% of the population in India has only access to primary care physicians and just 5% to specialists. The experts agreed that diagnosis can be done with simple tools. Developing a simple clinical checklist as a guidance tool focusing on clinical symptoms, medical history and sensory investigation and not requiring a lot of time, would improve the diagnosis of neuropathy by PCPs. Time is a critical factor in the healthcare system in India for both, patients and physicians.

To this end, the expert group proposed four basic steps in diagnosis of PN which can be used along with a simple sensory testing procedure (Table 2).

In the opinion of the experts, careful documentation of family, occupational, medical or previous treatment history as well as assessing any relevant drug abuse/addiction history and other factors are keyto identify the causative agents and aid in an accurate diagnosis (Step 1 – Table 2).

Presence of burning, tingling sensation or numbness in extremities indicates PN. Similarly, symptoms like hypersensitivity to touch, unsteady gait, history of fall, and presence of soreness/ulcer without any definite cause give cluestowards the diagnosis. Clinical signs differ depending on the impaired nerve which can be sensory, autonomic or motor nerves.Therefore, clinical evaluation of signs and symptoms was ascertained to be the next important step for diagnosis(Step 2.1 – Table 2).

Site and pattern of nerve involvement can also give a diagnostic clue to physicians. Nerve involvement can be single or multiple, large fiber or small fiberwhich have different conduction capacities.Localizing the pattern was also considered important by the expert group. For example, symmetrical distribution of symptoms would be a very typical sign of neuropathy (Step 2.2 – Table 2)[37].

The time line or the course of development of signs and symptoms classifies PN into three categories i.e. acute (<4 weeks), sub-acute (4-12 weeks) and chronic (>12

Table 1 — *Indicative list of causes of Peripheral Neuropathy in India*[1,17-35]

Disease-induced PN	Deficiency-induced PN	Drug-induced PN
• Diabetes (10-32%) • Guillian-Barre Syndrome (38.2-73.8%) • HIV (>50%) • Leprosy (4-8%) • Post-herpetic Neuralgia • Hypothyroidism • Glucose-intolerance • Chronic Kidney Disease (65%) • Carpel Tunnel Syndrome • Cancer-related neuropathy (15-50%) • Critical illness related Neuropathy (25-36%) • Chronic inflammatory demyelinating polyneuropathy • Vasculitic neuropathy - Rheumatoid arthritis (39.2%) - Systemic lupus erythematosus (3.3%)	PN caused by low levels of neurotropic B vitamins due to: • **Nutritional deficiencies** - Malnutrition - Vegetarianism - Tropical ataxic neuropathy - Deficiencies due to GI malabsorption • **Drug-induced deficiencies** ▪ Metformin-induced vitamin B12 deficiency ▪ Isoniazid-induced vitamin B6 deficiency ▪ Vitamin B3 deficiency due to Loop Diuretics ▪ Others	• Cardiovascular agents - Statins - amiodarone • Chemotherapy agents - Vince-alkaloids (vincristine, vinorelbine, etc) - Taxanes (paclitaxel, docetaxel) - Platinum compounds (cisplatin, oxaliplatin, carboplatin) • Antifungal agents-Triazoles (itraconazole, voriconazole)
Other causes		
• Heavy metals (such as lead, arsenic, mercury, etc) through - Environmental exposure - Herbal medicines • Organophosphates • Alcohol (13-66%) • Smoking (including passive smoking and chewing tobacco) • Hereditary Neuropathies - Charcot–Marie–Tooth disease (4.8%) - Amyloid neuropathy		

weeks). For example, vasculitis-related neuropathy presents as acute symptoms mostly within 1 to 3 days, symptoms of acute inflammatory demyelinating polyneuropathy (AIDP) peak within 4 weeks of onset, while chronic inflammatory demyelinating polyneuropathy (CIDP) takes more than 8 weeks. Experts recommended that understanding the course of the disease minimises diagnostic choices and, therefore, helps in accurate diagnosis and management procedure (Step 2.3 – Table 2).

Presently, standardised assessment tools are not available for diagnosis of PN in India. Expert group further recommended the inclusion of simple and easy to perform 2-minute sensory tests (Step 3 – Table 2) as a standard diagnostic procedure for PN which should be practical and feasible for all GPs. Sophisticated/ state of the art diagnostic or laboratory facilities may not be easily accessible in a resource-poor nation like India. The recommendation includes temperature and pinprick sensation assessment for small nerve fibre function and assessment of vibration sensation using 128 Hz tuning fork for large nerve fibres. Additionally, use of 10-g monofilament test for screening of large nerve fibre function in patients with diabetic neuropathy is also recommended. Physicians can even use very simple tools such as a cotton wool piece, small brush, toothpick, a wooden stick or a feather to test sensation impairment when they do not have a tuning fork or monofilament. These tests are in line with published literature where simple sensory tests and screening tools applied by general physicians have been used to facilitate preliminary assessment and for diagnosis of PN in the primary care setting[5,38-44]. In the current scenario, use of these simple tests/ screening tools was considered a practical solution for health care professionals at grass root level.

The final step recommended for diagnosis is to identify the cause of the presenting PN. It is important to determine the underlying cause and treat it accordingly in order to check the progression of symptoms and restrict further nerve damage (Step 4 - Table 2).

Table 2 — *Proposed Steps in Diagnosis of Peripheral Neuropathy for Clinical Practice in India*

Steps in diagnosis	Description
Step 1	**Careful analysis of medical history** (disease history, co-medications, etc) should be carried out. Examples of pertinent questions that should be asked are as follows (not an exhaustive list): • Is there a history of Diabetes in your family? • Is there a history of peripheral neuropathy in your family? • Do you use tobacco in any form? Smoking Bidis/cigarettes/tobacco containing chews/Khaini/Pan Masalas/tobacco containing tooth powders? • Do you use alcohol? How much and how often in a month? • Do you take medicines from Ayurvedic/Unani medical practioners? • What is your occupation? Is there any exposure to chemicals? • Are you exposed to toxin /heavy metal laden well water? • Is there a history of leprosy amongst your family/associates? • List the medications that you regularly use.
Step 2	**Checking for currently experienced symptoms, localisation of symptoms and determining time course**
2.1	Checking for symptoms experienced • Do you experience symptoms such as tingling, burning, numbness, etc in your upper or lower extremities (fingers, hands, toes, and feet)? • Do you feel pain even when lightly touched in a certain area? • Do you experience a sense of dizziness? Especially in the dark? • Have you had falls? • Do you feel hesitant or unsteady on walking? • Do you ever find blisters/sores/cracks/ulcers on your feet whose cause you do not know or which you did not notice when they developed? • Do you sometimes discover foreign objects in your shoes that you had not been aware of? • Any other unusual sensation (Please describe)
2.2	Localisation of symptoms, if reported • Are these symptoms in the upper or lower limbs, or both? • Can you draw the areas of your body where these sensations occur? (Human body sketch to be provided for shading in affected areas by the patient, as it is sometimes difficult for a patient to specify the location by verbal description) (Figure 1) • Are they on the right side or left side or both sides? • Do you ever feel difficulty in putting on your shoes or slippers?
2.3	Determining the time course of symptoms • When did you first experience the symptoms described by you? • Do these symptoms increase in cold weather/hot weather/summer/winter? • Has the intensity of these symptoms increased since their onset? • Are these symptoms persistent?
Step 3	**Conduct sensory testing** • Temperature or pinprick sensation (small fibre function) • Vibration sense using a 128Hz tuning fork; sensation test using a 10-g monofilament (large fibre function)
Step 4	**Identify probable cause(s) of the neuropathy, if possible** • Ascertain whether the neuropathy is due to existing systemic conditions (infections; other neurological conditions like GBS, etc; metabolic causes like diabetes, nutritional deficiencies, etc) • Determine if there might be deficiency of neurotropic vitamins on account of treatment-related factors such as use of metformin (diabetes), isoniazid (tuberculosis), etc • Look for nerve thickening/skin patches suggestive of leprosy • If the cause of neuropathy cannot be determined, consider specialist referral for further diagnosis

Given many cases of PN are a result of other systemic conditions, the importance of seeking expert help and accurate referral services for such patients cannot be denied[40]. In this context, the expert group proposed an algorithm incorporating diagnosis and referral services of patients suffering from PN with associated symptoms of neuropathic pain (Fig 2).

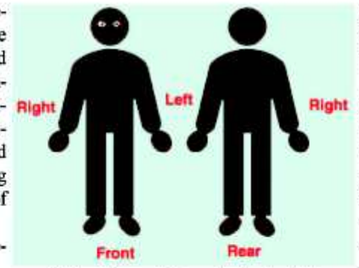

Fig 1 — Proposed Diagnostic Tool to Aid in Localization of Symptoms

Treatment and Prevention of Peripheral Neuropathy

Treatment of PN is still unclear for many GPs in India due to lack of well-structured treatment guidelines. Current international guidelines primarily focus on management of neuropathic pain, and not targeting the underlying cause of the disease. No guidelines exist for non-painful symptoms like tingling, numbness or autonomic symptoms etc. This leaves many PN patients unsatisfied and untreated, withpoor quality of life or treated with inappropriate agents[40,45,46].

The experts agreed that the guidelines for neuropathic pain management devised by international associations like American Diabetic Association (ADA) and International Association for the Study of Pain (IASP) are commonly being followed for managingpain associated with PN. However, these guidelines may not be fully applicable to the clinical practice in India due to issues pertaining to accessibility and/or cost of therapies. In addition, for a developing country like India, where toxic, infective and metabolic causes contribute heavily to the burden of neuropathy, treatment guidelines should take into consideration these elements as well. PN was recognised as one of the few conditions for which Indian clinical guidelines do not exist, and hence reinforced to the expert panel that an unmet need exists for guidance on the treatment and management of PN for GPs/PCPs across India.

Different recommendations from international organizations, like the Neuropathic Pain Specialist Interest Group of IASP (2007) and the European Federation of Neurologic Society (2010), suggest line-wise treatment modalities for neuropathic pain. They also recommend specific pharmacotherapies depending on different underlying causes of PN[47,48]. According to mentioned guidelines, first line treatment options are pregabalin and gabapentin, second line are tramadol and capsaicin 8% patch while opioids are used as a third line option. Worldwide, particularly in Western countries, the first line treatments are commonly used agents for the treatment of neuropathic pain. Similar clinical practice is followed in India as well, especially in patients treated by specialists. However, this differs from the situation in primary care where access to these treatment options might be limited.

The above referencedtreatment options offer effective symptomatic relief in most patients and focus on management of neuropathic pain. They do not contribute to restoration of nerve functionality and health. Additionally, numerous side effects have been found associated with the use of these medicines which can become a treatment burden for the patient.

It was agreed by the experts that instead of focusing on pain management, the primary goal should be to identify the cause of PN and treat the underlying aetiology. If the underlying cause is treated, like in cases of diabetic neuropathy, toxic exposure or vitamin B12 deficiency, further progression of the disease might be slowed down or even avoided. However, in cases where the cause cannot be identified, i.e. idiopathic PN, or in patients suffering from symptoms even after treatment, symptom management becomes the primary and the only approach to provide relief to the patients[49,50]. Nonetheless, in both scenarios, restoration of nerve health was agreed to be the next vital step in the treatment algorithm.

To this end, the experts highlighted the importance of alternative treatment options that include neurotropic B vitamins, alpha-lipoic acid (ALA) and other agents. These therapies have been shown to provide symptomatic relief in earlier stages of neuropathy, are well tolerated and additionally, play a significant role in nerve regeneration[11,51].

Alternative Treatment Options :

(1) Neurotropic B Vitamins

There was general consensus that the majority of physicians across relevant therapeutic disciplines are prescribing vitamin B combination products based on clinical experience of treating PN. Dosage, formulation and combi-

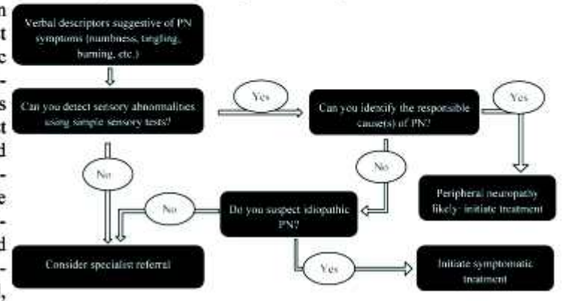

Fig 2 — Proposed Algorithm for Diagnosis and Referral of Patients presenting with Peripheral Neuropathy Symptoms in India

nation of B vitamins is selected on the basis of individual patient case requirements. The experts agreed on the benefits of using B -vitamin combination over mono-therapy approaches specifically complexes of B1/B6/B12 as these three vitamins are documented to play an important role in nerve health and are well-established globally for treatment of PN.

Vitamin B12 (cobalamin) improves the symptom of PN by regenerating or re-myelinating nerves through increased protein synthesis. Selective blockade of sensory nerve conduction by vitamin B12 also helps in alleviating the symptoms[52]. Deficiency of vitamin B12 has been shown to result in increased levels of neurotoxic cytokine TNF-alpha and decreased levels of neurotropic epidermal growth factor and neurotropic cytokine IL6 leading to PN symptoms[53]. Supplementation by vitamin B12 corrects the deficiency and benefits PN patients. Studies on vitamins like vitamin B1 (thiamin) and B6 (pyridoxine) also suggest their role in PN[51,54-58]. Biochemically, vitamin B1 acts through diacylglycerol protein kinase C pathway, glycation end-product formation pathway and the hexamine pathway to reduce pain. It also modulates neural excitability and Na+ currents in injured dorsal root ganglions to improve symptoms of neuropathy[59-61]. Role of vitamin B6 in PN includes inhibition of presynaptic transmitter release from nociceptive afferent fibres carrying excitatory input to the spinal dorsal horn and thalamic neurons[62]. Vitamins B1, B6 and B12 act synergistically in terms of their mechanism of action, thus complementing the neurotropic activity of each other. Use of combination of these neurotropic vitamins has been shown to improve the nerve conduction velocity and also improves the vibration threshold[63]. The fixed dose combination of these vitamins has been found to be well-tolerated and effective for the treatment of mild to moderate PN of various aetiologies[64]. Evidence suggests thatcombination use of vitamin B1, B6 and B12, was also efficacious in more than 80% of cases of diabetic neuropathy[65,66].

Posology of Neurotropic B Vitamins

The expert group recommended that parenteral approaches such as injectable formats be prescribed for the treatment of hospitalized patients with neuropathy eg, diabetic PN[67] and acute PN symptoms. Similarlyuseful for patients with neurological symptoms related to acute neuralgia eg, trigeminal or plantar neuralgia[68], acute symptoms related to herpes zoster, lumbago, sciatica, shoulder-arm syndrome[52], diabetic cranial neuropathy and neuropathic pain associated with cancer pain/cancer treatment or in any other case where rapid relief is required. In addition, injectable is preferred in patients with impaired absorption due to gastrointestinal disorders such as Irritable Bowel Syndrome (IBS), colitis, H pylori infection, gastritis etc[69,70] to ensure a fast restoration of B vitamin levels. However, evidence shows that high dose oral vitamin application can also restore the levels as effectively as injections[71]. In various studies, oral dosages of 1500 mcg and higher were found to be therapeutically useful[11,64,70,72]. The decision to administer injectable and/or oral therapy should lie with the PCP based on their assessment of what will work best for patients based on their current status and the desired

Table 3 — *Recommendations for Prophylactic, Therapeutic and Maintenance Therapies of Peripheral Neuropathy Patients*

		Prophylactic	Therapeutic	Maintenance
Diabetic Patients	Patient Segment	• Patients at risk of developing PN, currently not showing PN symptoms, including: • Asymptomatic patients, at high risk of vitamin B deficiency • Asymptomatic patients who frequently take tuberculosis drugs which cause deficiency • Orthopedic patients, facing mild symptoms related to sciatica pain, low back pain, CTS • Older patients • Alcoholics	• Patients presenting acute/moderate to severe symptoms of neuropathy - With neuropathic pain - Without neuropathic pain, but present moderate-to-severe numbness, burning, tingling, atrophy, etc. • Patients hospitalized due to neuropathy • Patients with mild-to-moderate symptoms	• Patients who feel better with PN treatment, may be still suffer from mild-to-moderate symptoms • Patients who have been cured and want to avoid reappearance of PN symptoms • Chronic or acute PN patients with mild symptoms
	Recommendation	• Low therapeutic dose of neurotropic B vitamins • Low dose of other alternative therapies	• For neuropathic pain relief, pregabalin or gabapentin as first line. • Therapeutic doses of neurotropic B vitamins: - Injectable is preferred in acute cases or GI malabsorption or more control is needed (e.g. a rural primary care center) - In other cases, orals with high dose neurotropic B vitamins • High dose of other alternative therapies	• Maintenance dose of neurotropic B vitamins (preferably orals) or other treatment options
	Patient Segment	• Patients diagnosed with pre-diabetes • Asymptomatic patients taking metformin • Asymptomatic patients, at risk of vitamin B deficiency	• Patients presenting acute/moderate to severe symptoms of neuropathy - With neuropathic pain - Without neuropathic pain, but moderate-to-severe numbness, burning, tingling, etc. • Patients hospitalized due to neuropathy • Patients with mild-to-moderate symptoms	• Patients who feel better with PN treatment, but still suffer from mild-to-moderate symptoms • Patients who have been cured and want to avoid reappearance of PN symptoms • Chronic PN patients with mild symptoms
	Recommendation	• Low dose of neurotropic B vitamins • Low dose ALA (100mg daily), especially recommendable in patients with high CVD risk • Low dose of other alternative therapies	• For neuropathic pain relief, pregabalin or gabapentin as first line. • Therapeutic doses of neurotropic B vitamins: - Injectable is preferred in acute cases or GI malabsorption or more control is needed (e.g. a rural primary care center) - In other cases, orals with high dose neurotropic B vitamins • Therapeutic dose of ALA (600mg daily) • High dose of other alternative therapies	• Maintenance dose of neurotropic B vitamins (preferably orals) or other treatment options • Maintenance dose of ALA (100-300mg daily)

*Experts recommended prescribing ALA to non-diabetics patients also, owing to its anti-oxidative properties.

Note : Dose, treatment duration, formulation is as directed by the physician.

outcome. PCPs can ensure better compliance control (eg, a rural primary care centres) with injectable formulations and in cases where they do not foreseeproblems with compliance, oral pills can be prescribed. In other mild-to-moderate cases of PN, oral doses of vitamin B12 in the range of 1000-1500 mcg are able to impart therapeutic effect[73-76].

In cases of chronic conditions leading to neuropathy, like diabetes, the dosing pattern can determine the patient's adherence to medications. Long term diabetic patients may require multiple dosing of diabetic medications. In addition, they may also require additional drugs like anti-hypertensive orcholesterol reducing agents etc. depending on associated co-morbidities. Further addition of multiple dose schedule of neurotropic vitamins can hamper compliance[77]. In clinical practice, it is seen that prescribing vitamin B 12 (500 mcg) thrice daily (TID) decreases compliance after 6 months. The twice daily (750 mcg) (BD) regimen improves compliance while once daily (1500 mcg) (OD) dosing demonstrates highest patient compliance. It was recommended to give multiple dose of vitamin B12 during the treatment period followed by single dose regimen for maintenance.

Monitoring of Neurotropic B Vitamin Levels

Regular follow-up and monitoring of patients taking higher doses of vitamin B6 (>50 mg) for periods of more than 6 months is recommended.In various long-term clinical studies, it was established that both vitamins B1 (100 mg/day or more)[67,78,79] and B12 (up to 6000 mcg/day)[80,81] have favourable safety profile and are very well tolerated over a long treatment period. No upper limits (UL) are established for vitamin B1 and B12. (82) However, in clinical practice in India, a safety concern exists among PCPs while prescribing prolonged high vitamin B12 doses (>2000 mcg). The experts recommend monitoring the patient with a high dose therapy for any side effects and potentially of vitamin B12 levels if the patient experiences any side-effects with prolonged use. The panel recommended Mean Corpuscular Volume (MCV) as an efficient, reliable and cost effective test in quantifying vitamin B12 level in the body instead of assessment of serum vitamin B12 for diagnosis and monitoring[83].

The experts agreed that guidance on the correct dose, duration of use and even combination of B vitamins should be provided based on general patient type and associated clinical status e.g. acute vs chronic[24,84]. Additionally, the expert group suggested prophylactic, therapeutic and maintenance usage in different patient settings (Table 3).

(2) Alpha-Lipoic Acid (ALA) in Treatment of PN

Evidence from clinical trials suggest that diabetic patients with neuropathy treated with ALA daily have reduced numbness, pain and paraesthesia. ALA is discussed to improve insulin sensitivity and is therefore most suitable for diabetic PN patients[85]. ALA can also reduce levels of interleukin 6 and plasminogen activator 1 in plasma, suggesting that it may improve endothelial dysfunction through anti-inflammatory and anti-thrombotic mechanisms. It is notable that ALA may improve nitric oxide-mediated endothelium-dependent vasodilation in diabetic patients[86]. ALA may also have the potential beneficial effect in cases with high CVD risk, by decreasing the plasma level of ADMAconsidering that ADMA is an independent risk factor for cardiovascular outcome in ESRD patients[87].

Posology of ALA

A meta-analysis from 6 randomised controlled trials concluded that ALA, administered intravenously for 3 weeks at a strength of 600 mg per day, resulted in significant clinical improvement[88]. Additionally, an oral dose of 600 mg /day is also reported to have the optimal risk/benefit ratio[89,90]. Evidence exists which indicates that 300 mg ALA is capable of exerting a therapeutic effect and benefit has also been observed with doses of more than 600 mg, administered orally for at least 5-8 weeks[88,91-93]. However, high ALA dose (>600 mg/day) has been found to increase gastrointestinal side effects like nausea, vomiting and dizziness[73,88,91]. During the sub-acute or chronic phase, maintenance dose of 300 mg could be used. In line with current evidence, expert group suggested that ALA should be prescribed alone or in combination with vitamin B12 for diabetic PN (Table 3). Experts were in consensus that patients with acute diabetic neuropathy should be prescribed 600 mg ALA initially for 3-months duration followed by 100-300mg ALA in maintenance. It is important to note that the 100 mg dose of ALA is prescribed only during maintenance for its anti-oxidative neuro-protective benefits and not for therapeutic benefit.

It has been observed that ALA is also prescribed to non-diabetics in practice primarily owing to its anti-oxidant properties. However, there is a dearth of scientific evidence for the effective use of ALA in non-diabetics.

(3) Other Alternative Treatments for PN

In addition to the above listed therapies, several other alternative treatments have been identified and with varied efficacies established in different PN patient segmentsthrough various clinical studies. The potential mechanisms by which these therapies act, include deficiency correction, oxidative stress reduction, nerve growth factor stimulation etc[11]. Therapies like Acetyl-L-Carnitine, opioids, botulinum toxin A, mexidol, reflexology etc., have shown improvements in diabetic PN symptoms in some studies[11,92,93]. Preliminary studies with therapies involving treatment or supplementation with Acetyl-L-Carnitine, vitamin E, minerals like calcium and magnesium, glutathione, glutamine, N-Acetyl-Cysteine etc have also shown positive results for chemotherapy-induced PN[11,94,95].

Vitamin B Deficiency :

The experts acknowledged that Indian patients are likely to have deficiencies for multiple B vitamins owing to various underlying causes including malnutrition, veg-

etarianism, alcoholism and drug-induced or 'iatrogenic' causes(due to a disease) eg pernicious anemia[96]. The clinical manifestations for vitamin B deficiency varies drastically from mild conditions such as neuropathy with symptoms like ataxia, sensation disturbance, weakness, etc. to more severe disorders such as combined sclerosis of the spinal cord, haemolytic anaemia and even pancytopenia[96].

Although India is taking several measures to fight against malnutrition, micronutrient deficiency is widespread in India. In 38.7% of Indian children aged 0–59 months are stunted, and stunting is prevalent across all socioeconomic groups. 44–66% of the affluent schoolchildren had vitamin A, B2, B6, B12, and C deficiencies[97]. Median intakes of all nutrients, except vitamin B1, were below the RDAs for Indians. Another significant reason of high prevalence of vitamin B deficiencies in India is the significantly higher number of vegetarians as compared to other western countries[51,69,98].

Chronic diabetes or gastritis patients are very often poly-medicated; intake of several active ingredients can lead to drug-interactions leading to vitamin B deficiency. Long-term use of metformin, widely used as a first-line treatment for type 2 diabetes in India, can cause vitamin B12 deficiency[28-30,54,96,99,100]. Therefore, metformin treatment should be supplemented with an adequate dose of vitamin B12in type 2 diabetes patients. Tuberculosis (TB) drugs likeisoniazidare linked with vitamin B6 deficiency. According to World Health Organization TB Statistics, 2.79 million new TB cases, ~27% of worldwide new cases, were estimated in 2016[101], indicating a very heavy usage of TB drugs in India. Use of H2-antagonists such as ranitidine, cimetidine and proton pump inhibitors such as omeprazole are significantly associated with vitamin B12 deficiency[102]. Prolonged treatment with loop diuretics is associated with urinary loss of vitamin B1 and deficiency[31]. Treatment with anticonvulsants including phenobarbital, primidone, pregabalin andtopiramate is associated with vitamin B6 and B12 deficiency[103,104]. Vitamin B12 deficiency is common in patients with pernicious anaemia and elderly patients and its incidence increases with age[95].

A significant portion of the Indian population is at high risk of developing deficiencies of multiple B vitamins, and therefore, remains at risk of developing PN and should be monitored carefully.

While vitamin B12 can be measured through tests, those for measuring vitamin B1 and B6 are either not accessible for the patient due to availability or costs or not established. The experts agreed on the benefits of using combination of B1/B6/B12 vitamins in patients where a deficiency is suspected due to a present risk, symptoms or other factorsas cautionary measure even without quantifying levels in order to prevent further development of diseases affecting the nervous system or other health areas.

Conclusion :

The burden of PN in India is significant due to higher prevalence of diabetes cases, nutritional deficiencies, infectious diseases, and exposure to toxic substance in India as compared to developed countries. In light of this fact, primary care physicians should carefully evaluate underlying causes by documenting complete patient history and utilizing available diagnostic facilities to confirm diagnosis of PN. Management should be focussed on treating the underlying cause and symptomatic relief, followed by restoration of nerve health.First line pharmacological treatments like pregabalin and gabapentin show a higher efficacy in neuropathic pain, and expert group was in consensus that judicial use of these drugs will definitely ameliorate neuropathic pain symptoms. Neurotropic vitamins like vitamin B1, vitamin B6 and, most importantly, vitamin B12 are recommended in the treatment of PN, considering their role in nerve regeneration. Alpha-lipoic acid is also considered effective in treatment especially in DPN, owing to its antioxidant properties.

This advisory board meeting was an initial yet important step towards bringing multi-disciplinary experts on a common platform to discuss the management of PN in India. While the meeting outcomes provided useful guidance on PN diagnosis, treatment and management, more of such experience-based cross-speciality deliberations are required to formulate holistic guidelines for the management and treatment of PN in India.

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Review Article

Short stature — clinical approach to diagnosis : a 2018 perspective

Vineet Surana[1], Rajiv Singla[2], Sameer Aggarwal[3], Deepak Khandelwal[4], Saptarshi Bhattacharya[5], Sanjay Kalra[6], Deep Dutta[7]

Concern for linear growth or short stature is unequivocally the most common pediatric endocrine problem. Growth in children is complex and predictable at same time. It is easy to detect any deviation from normal growth in children, but at the same time reaching an etiological diagnosis for same may be quite challenging and a daunting task. Nonetheless, reaching a diagnosis and institution of prompt treatment can be equally rewarding. Chronic systemic diseases are the most common cause for short stature in India, but endocrine diseases are being increasingly diagnosed. A systematic, but practical, approach is required to ascertain the cause of growth retardation in children.

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Key words **: Short Stature, Growth Stature Deficiency, Evaluation.**

Growth is a fundamental and inherent indicator of child hood and adolescence health. Even though the process of growth is multifactorial and complex, children usually grow in a remarkably predictable manner. Deviation from such a normal pattern of growth can be the first manifestation of a wide variety of disease processes, including endocrine and non-endocrine disorders and virtually involving any organ system of the body[1]. Growth retardation not only affect physical appearance of child but also lead to poor health related quality of life score and also various parents reported psychosocial problems. Treatment of children with short stature lead to better health related quality of life score[2]. Short stature or growth retardation is regarded as relatively early sign of poor health.3Hence monitoring of growth becomes utmost important and it is relevant to answer 3 simple questions while evaluating a child with short stature.

(1) Is child short?

(2) Is it physiological or pathological growth retardation?

(3) What is a probable etiology?

This article intends to give practical clinical pathways to evaluate any child suspected to have short stature.

[1]MD, DM, Senior Consultant, Department of Endocrinology, Manipal Hospital, Dwarka, New Delhi 110078
[2]MD, DM, Senior Consultant, Department of Endocrinology, Kalpavriksh Healthcare, Dwarka, New Delhi 110078
[3]MD, DM, Senior Consultant & Head, Department of Endocrinology & Metabolism, Apex Plus Superspeciality Hospital, Rohtak 124001
[4]MD, DM, Senior Consultant, Department of Endocrinology, Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi 110026
[5]MD, DM, Senior Consultant, Department of Endocrinology, Max Superspecialty Hospitals, Patparganj, New Delhi 110092
[6]MD, DM, Senior Consultant, Department of Endocrinology, Bharti Hospital, Karnal 132001
[7]MD, DM, Senior Consultant, Department of Endocrinology, Venkateshwar Hospitals, Dwarka, New Delhi, 110075 and Corresponding author

Materials and Methods

PubMed, Medline, and Embase search for articles published to April 2018, using the terms "short stature" [MeSH Terms] OR "short height" [All Fields] OR "growth hormone" [All Fields]. The references of the articles obtained from this search were also reviewed. The search was not limited to English language literature.

Results

Normal Growth Physiology :

Linear growth in human beings can be divided into four phases: 4 intrauterine, infantile, prepubertal and pubertal. Male and female siblings usually differ by 13 cm in final growth. This difference is contributed by late onset of puberty[5] and more height gained in pubertal growth spurt in males[6].

In nine months of intrauterine growth, a child grows by 50 cm, making it the fastest phase of growth in human lifespan. Growth in intrauterine life is affected largely by maternal factors and to a lesser extent by genetic make-up of child. These factors include maternal nutrition, placental size and function[8], maternal smoking, maternal age, birth order and genetic structure of child[7]. Presence of any of these factors can result in short-for-gestational-age babies. Endocrine factors do not seem to affect growth tremendously in this phase. First trimester growth is predominantly affected by genetic make up of child whereas subsequent growth is determined by both maternal as well as hormonal factors of fetus including pregnancy-associated plasma protein A (PPAPA),insulin like growth factor 2 (IGF2) and insulin like growth factor 1 (IGF1)[8]. First trimester growth is predominantly related to organogenesis. Second trimester is the fastest growing phase in any one's life where fetus gains maximum length whereas 3rd trimester results in acquisition of body weight.

Infantile growth is again significantly contributed by nutritional status[9]. Presence of normal levels of growth hormone and thyroid hormone is permissive and essential for this phase of growth. Role of sex steroids during mini-puberty on linear growth has not been well studied and probably play a minor role only. Children typically grow by 25 cm in first year of life and 12 cm in second year.A child achieves a predictable channel (percentile) of growth by end of infancy[9] and follows the same channel during childhood to achieve genetically determined target height. After first two years of life, growth is usually 6-7 cm per year[10]. This childhood, also known as pre-pubertal, growth phase is predominantly due to growth hormone[11] and thyroxin[12,13] has a permissive role. Nutritional status can affect growth in this phase by hypothalamic suppression, by inducing secondary growth hormone resistance in case of malnutrition or by affecting timing of onset of puberty in case of obesity.

Pubertal growth spurt is driven by sex steroids by either direct action on epiphysis[12] or indirectly by increasing IGF 1 production locally at growth plate[14,15]. Presence of normal growth hormone is essential in this phase also. Any disease condition affecting either gonadal axis or growth hormone axis would also impair pubertal growth spurt. Child with low sex steroid would still continue to grow at pre-pubertal phase, while child with deficient growth hormone would typically have growth rate lower than six centimeter per year. Height gained during pubertal growth spurt is usually 20-30 centimeter. Onset of pubertal growth spurt correlates more closely with bone age than either chronologic age or height age. Females have growth spurt at bone age of 12 years and males have it at 13 years bone age[16].

Terminologies :

It is essential to know about exact meaning of different terminologies used during work up of a case of short stature. This is of paramount importance in case the patient follows up with another clinician. Common terms used are described in Table 1.

When to Evaluate :

Children, usually, follow centile curves on their growth chart according to mean parental height. Any child should be evaluated for growth retardation if he is deviating significantly from his/her growth curve observed over a period of time. This can be done by using either centiles or standard deviation scores (SDS). SDS is calculated as difference in observed minus expected height of patient and divided by standard deviation (SD) of population mean[17]. Specific cut-offs, for evaluation, have been used in different national programs, but they are for guidance only and each patient is to be evaluated individually.

There are few guidelines regarding when to start diagnostic work up of children with short stature. Oldest of them is Finnish guideline[17] which was based on longitudinal studies of normal children. This guideline suggests the cutoff limits for height of child based on height and target height SDS of ±2.3. Other guidelines, from UK34 and Dutch,18 were based on consensus meeting. UK guidelines, alsoknown as Coventry consensus, stress on single measurement of height at school entry at 5 year of age. Evaluation of short stature is recommended if child's height is < 0.4 centile of corresponding UK normative data. However, it does not consider MPH, Growth velocity, and child who are short stature at or below 5 years of age.

Dutch guidelines[19], which were published in 1998, included three referral criteria: height SDS, change in height SDS, and difference between height SDS and target height SDS. In another guideline[20] publishedin 2008, children less than 3 years of age need to be evaluated are with extremely low or repetitive low height SDS. For children between 3 to 10 years, short for target height rule (height SDS minus target height SDS < 2) and height SDS < 2 should be the trigger for further evaluation.

Consensus Guidelines for diagnosis and therapy of GHD issued by GH research society[21] in 2000 also give criteria for immediate evaluation of children with suspected GHD, which includes : (a) Severe short stature, defined as a height more than 3 SDS below the mean. (b) Height more than 1.5 SDS below the mid- parental height. (c) Height more than 2 SDS below the mean and a height velocity over 1 year more than 1 SDS below the mean for chronological age, or a decrease in height SDS of more than 0.5 over 1 year in children over 2 year of age. (d) In the absence of short stature, a height velocity more than 2 SDS below the mean over 1

Table 1 — *Terminologies used in evaluation of a case of short stature*

Mid parental height (MPH) is mean of maternal and paternal height.
Target height is MPH plus 6.5 centimeter for male child and MPH minus 6.5 centimeter for female child.
Target height range has been defined variably in literature and is target height ± 8-10 centimeter. Target height range corresponds to two standard deviations from target height[28].
Bone age refers to maturation of bones as assessed by comparing x-ray of left hand (by convention) with reference x-rays/method e.g. Grulich and Pyle atlas or TW3 method. Correct estimation of bone age is most important step in evaluation of a case of short stature.
Height age is defined as age at which current height should correspond to 50th centile for that age.
Chronological age is defined as actual age of child as per his date of birth
Growth velocity is rate of linear growth and is expressed as growth over preceding one year. Minimum period required to assess growth velocity is six months because growth rate is not uniform over one year. Children may have period of saltation with excessive growth alternating with period of stasis with slow or even nil growth over 2-3 months. Seasonal variation should also be kept in mind while analyzing growth velocity; children may grow more during spring season[29].

year or more than 1.5 SDS sustained over 2 year.

However, each child needs to be treated individually based on various circumstances. In our country, we usually follow GH research society criteria. Table 2 summarizes the guidelines available in literature for screening of children for short stature.

Classification of Short Stature :

Short stature can be classified in two ways. One classification is based on relationship of height age, chronological age and bone age, whichis more helpful in day to day practice whereas another isetiology based classification as suggested by European Society for Paediatric Endocrinology (ESPE)[22]. A child can be divided into one of three categoriesof short stature as intrinsic vs delayed vs attenuated growth which is predominantly decided by relationship between bone age (BA), height age (HA), chronological age (CA) and growth velocity. A child with CA=BA>HA with normal growth velocity would be classified as intrinsic shortness. A child with BA<CA with normal growth velocity will be divided two groups either delayed growth with normal growth velocity or attenuated growth with subnormal growth velocity[23]. Classifying a short child in one of these categories may narrow the spectrum of investigations required to reach an etiological diagnosis.

Another way to classify growth disorder can be adopted from ESPE classification of Paediatric Endocrine Diagnoses, where growth disorders are classified into 3 main groups[24].

(A) Primary growth disorders (conditions thought to be intrinsic to the growth plate) : This condition includes all condition associated with intrinsic shortness and includes genetic syndromes, short foe gestational age children and skeletal dysplasias.

(B) Secondary growth disorders (conditions that change the milieu of the growth plates): All other endocrine and systemic diseases are categorized as cause of secondary growth failure. They can present as delayed growth or as attenuated growth pattern. For example, a compensated systemic condition can lead to initial lag and followed by sustained growth at low-normal rate resulting in delayed pattern of growth. While, most of endocrine diseases present as attenuated growth failure.

(C) Idiopathic short stature (no recognizable cause is found): Idiopathic short stature (ISS) is subdivided into familial and non-familial short stature, and both can be further subcategorized into children with delayed and normal puberty.

Table 2 — *Summary of various guidelines for screening of children for short stature*

Guideline	Methodology	Recommendation for evaluation
Finnish[31]	Longitudinal	Height and target height SDS of -2.3
UK[34]	Consensus	Single measurement at 5 years of age. If height < 0.4 centile
Dutch[35]	Consensus	Based on height SDS, target height SDS and diff between both
Dutch (2008)[36]	Longitudinal	<3 year repetitive low height SDS 3-10 years < 2SDS
GH research society[37]	Consensus	• Height > 3 SDS below the mean • Height > 1.5 SDS below MPH • Decrease in Height velocity > 0.5 SDS over 1 year • Height velocity > 2 SDS below mean over 1 year

UK = United Kingdom, MPH = Mid parental height, GH = growth hormone

Evaluation of Short Stature :

The first step towards evaluation of these children is to determine whether the child is actually short for his parental height or not as almost 90 percent of children referred for evaluation of short stature may not be short and even children who are short almost 40 percent can be of normal variant[25].

The evaluation starts with a detailed clinical history (Table 3)[26]. A complete meticulous examination (Table 4) of child is of utmost importance in finding out etiology of short stature. Height should be ideally measured by same appropriately calibrated stadiometer each time to avoid instrumental variability in height. Child should stand on stadiometer in such a way that heel, buttock and occiput should touch the back of stadiometer and head should be positioned in Frankfurt plane. For children less than two years of age, infantometer should be used. Pubertal staging is essential part of examination. Sitting height should be measured in each child to calculate Upper segment (US) and lower Segment (LS). A disproportionate short stature can be due to different etiologies as mentioned in Table 5. Though difficult, certain features can help in differentiating between constitutional delay in growth and puberty, familial short stature and growth hormone deficiency (Table 6).

Growth charts: The most critical factor in evaluating the growth of a child is to determine the growth velocity. Serial plot of a height on the growth chart provides a valuable clue for identifying early growth retardation. However at least a period of 6 month is required to meaningfully determine growth velocity. Height determination in relation to age, sex, pubertal status, genetic potential, and population norm and in certain situations to syndrome specific growth curves (eg, Turner syndrome)[27] is indispensable. Deviation of growth from the appropriate disease related growth curve suggests the possibility of a second underlying cause, such as acquired autoimmune hypothyroidism in children with Down syndrome or Turner syndrome. There are various charts available for height plotting like CDC charts, KN Agarwal chart, WHO charts, Marwaha et al charts[28] and IAP charts[29] in our country. It is always confusing which charts to be used and plotting on two different charts can give different results[30]. IAP recommends to use WHO growth chart for children less than 5 year. For children between 5 to 18 years Revised IAP growth

Table 3 — *History in child with short stature*

History	Diagnosis
Maternal drug exposure (alcohol, phenytoin), maternal smoking,	Fetal alcohol syndrome, fetal hydantoin syndrome,
Maternal PIH, GDM, abruption placentae,	IUGR
Family h/o short stature	Familial short stature, CDGP
Neonatal hypoglycemia, prolonged neonatal jaundice, small size phallus	GHD, Hypothyroidism, Hypopituitarism
Recurrent respiratory complaints	Childhood asthma, cystic fibrosis, tuberculosis, Congenital Heart Disease
Chronic ear discharge	ASOM, CSOM, Turner Syndrome
Recurrent diarrhea, vomiting	Chronic gastrointestinal malabsorption syndrome, Celiac disease, Congenital adrenal hyperplasia
Blood transfusion	Malabsorption, PEM, thalassemia, sickle cell anemia, Celiac disease
Cyanosis, Dyspnea	Congenital Heart Disease
Recurrent jaundice, ascites	Chronic Liver Disease
Recurrent Urinary tract infection(UTI), ascites, oliguria, proteinuria	UTI, congenital urogenital system abnormality like vesicoureteric reflux, malformed kidney etc. Nephrotic syndrome
Salt craving, polyuria	Renal Tubular Acidosis
Bony deformity, h/s/o proximal muscle weakness, h/o dental abnormalities, h/o bone pain	Rickets and its various etiology
Head trauma, breach delivery, cranial irradiation, meningoencephalitis, visual difficulty, headache, Diabetes insipidus like features	GHD, panhypopituitarism, intracranial neoplasm like craniopharyngioma
Chronic steroid intake	Iatrogenic Cushing syndrome
Psychosocial history like binging, purging and altered body image	Anorexia Nervosa, Bulimia Nervosa

PIH = pregnancy induced hypertension, GDM = gestational diabetes mellitus, IUGR = Intrauterine growth retardation, CDGP = Constitutional delay in growth and puberty, GHD = growth hormone deficiency, ASOM = acute suppurative otitis media, CSOM = chronic suppurative otitis media, PEM = protein energy malnutrition

chart[31] or recent most published population specific charts should be used. However periodic update of these charts (at least every decade) are recommended to accommodate the changing socioeconomic scenario of population.

The first basic investigation in assessment of short child is to get X ray of left hand with wrist[31]and correct estimation of bone age by either Grulich and Pyle atlas or Tanners Whitehouse-3 (TW3) method. Counting the number of carpal bones is an inaccurate method for calculation of BA and should not be done. In infants less than 1 year, bone age may be estimated from radiographs of knee and ankle.

The initial baseline investigations have been elaborated in Table 7.CBC is done to look for evidence and type of anemia.Urine pH is must to look for evidence of renal tubular acidosis (RTA).Based on the analysis of 12 studies Van Rijn *et al*[32] concluded that in 2-8% of children presenting with only short stature (in the absence of typical gastrointestinal symptoms), celiac disease might be the underlying cause; whereas if we exclude other causes for short stature, this risk increases to 19-59%. Data from our country suggest prevalence of 11% celiac disease in children of short stature in institution based study with chronic diarrhea and anemia being significant predictor[33]. Hence all children with short stature should be evaluated for celiac disease. T4 and TSH34 should be done to rule out hypothyroidism. Girls with no other explanation for short stature should undergo karyotyping to exclude Turner syndrome, even in the absence of other features, as short stature may be the only presentation of Turner syndrome[35].

If no cause is identified on above investigation and there is strong suspicion of growth hormone deficiency (GHD),an IGF136,37level should be done. A normal age and sex matched IGF 1 level essentially rules out GHD however few of mild GHD may be missed. A low IGF 1 level is very much in favor of GHD but it does not confirm the diagnosis of GHD.38However IGF 1 level estimation has its own problem as result need to be correlated with age and sex matched normative data, which is not available for most of countries, including India. Low IGF 1 level can also be seen in acquired GH resistance state like malnutrition[39], hypothyroidism[40], chronic inflammatory conditions, organ failure like hepatic[41] and renal failure[42].

Table 4 — *Examination findings in child with short stature*

Findings	Diagnosis
Evidence of malnutrition like dull lusterless hair, cheilitis, stomatitis, pallor, bitots spots, dry skin, loss of subcutaneous fat	PEM, malabsorption disorders
Dysmorphic features	Syndromic etiology
Hypertension	CHD like coarcation of aorta, CKD, cushing syndrome
Goiter, bradycardia, dry skin	Hypothyroidism
Rachitic changes likes wrist widening, rachitic rosary, frontal bossing, Harrison sulcus	Rickets
Heart murmurs	CHD
Wheeze, crepitation	Asthma, cystic fibrosis
Organomegaly	CLD, storage disorders, chronic infections
Overweight/ obese	Hypothyroidism, Cushing's syndrome, GHD, Pseudohypoparathyroidism
Hypotonia	Muscle disorder
Sign of neglect or abuse	Emotional deprivation
Disproportionate anthropometry, blue sclera	Skeletal dysplasia, `Osteogenesis imperfecta

PEM = protein energy malnutrition, CHD = Congenital heart disease, CKD = chronic kidney disease, CLD = Chronic liver disease, GHD = growth hormone deficiency

Table 5 — *Etiology of disproportionate short stature*

US>LS	LS>US
Achondroplasia	Spondyloepiphyseal dysplasia
Hypochondroplasia	Hemivertebrae
Chondro dysplasia punctate	Caries spine
Rickets	Mucopolysachroidosis
Osteogenesis imperfect	Mucolipidosis
Hypothyroidism	

US = Upper segment, LS = lower segment

Table 6 — *Differential features in CDGP versus Familial versus GHD*

Features	CDGP	Familial	GHD
Clinical	Short stature	Short stature	May have h/o hypoglycemia, midline defect, micropenis,
Endocrine	None	None	Other pituitary hormone deficiency
Bone age	Delayed	Normal	Delayed
Pubertal status	Delayed	Normal	Normal/delayed
Neuro-Imaging	Normal	Normal	Normal/Abnormal
Growth hormone stimulation test	Normal/ sometime abnormal	Normal	Abnormal

CDGP=Constitutional delay in growth and puberty, GHD=Growth hormone deficiency

Table 7 — *Investigations in evaluations of short stature*

Investigation	Diagnosis/clues towards diagnosis
Hemogram	Nutritional anemia, chronic anemia like thalassemia, sickle cell anemia, Celiac disease, chronic inflammatory disorders, chronic infections
Erythrocyte sedimentation rate	IBD, chronic infections
KFT	CKD
Electrolytes, urine PH	Renal tubular acidosis
Calcium, phosphate, ALP	Various etiology of Rickets
LFT	CLD
Urine routine and microscopy	Occult UTI, Renal tubular disorders
T4/TSH	Hypothyroidism
S IgA TTG	Celiac disease
X ray Skull	Craniopharyngioma, sellar mass
X ray Wrist with hand	Bone age, e/o rickets, skeletal dysplasia
Echocardiography	Congenital heart disease
Karyotype	Turner syndrome and other syndromic etiologies of short stature

IBD = inflammatory bowel disease, KFT = kidney function test, CKD = chronic kidney disease, ALP = alkaline phosphatase, LFT = liver function test, CLD = Chronic liver disease, UTI = Urinary tract infection, TTG = tissue transglutaminase,

Children with poorly controlled T1DM also have low normal IGF1 but this rise to normal level once adequately treated[43]. The role of IGFBP3 in diagnosis of GHD is controversial in children more than 3 years of age however it is recommended in children less than 3 years of age[44]. IGFBP3 enjoys advantage of being GH dependent and has less variability with nutrition and age. Like IGF1, IGFBP3 level also does not have diurnal variation. IGFBP3 has good specificity and low level of IGFBP3 support diagnosis of GHD. However, in a study by Cianfarani *et al*, sensitivity of IGFBP3 was just 27 percent making it an imperfect tool in screening of GHD[44].

Growth Hormone Stimulation Test (GHST) :

Growth hormone stimulation testsare used as provocative testing tool for diagnosis of GHD. As, GH is predominantly secreted overnight in a pulsatile manner, with concentrations normally undetectable during the day, single random measurement of GH is of no value, except in neonates, in whom a random GH of <20 ng/ml is suggestive of GHD.Hence, a variety of GHST (Table 8), both physiological (such as sleep, exercise) and pharmacological (such as glucagon, insulin, arginine and clonidine) have been developed to determine an individual's capacity for GH secretion.Two or more provocative tests areto be done to confirm subnormal response, as 15-20% of normal children can have a subnormal response to single test[27]. However, single test would suffice for patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiencies (MPHD) or a genetic defect known to be associated with GHD. The commonly used methods are clonidine stimulation test,insulin tolerance test (ITT) and glucagon stimulation test[45,46]. These tests are carried out in the morning after overnight fast using a standardized protocol. As child will require close observation for up to 2-3 hours after the test; a short admission is advisable for doing GHST.Severe/complete GHD is defined as peak GH value of <5 ng/ml after provocative testing and moderate/ partial GHD as peak GH <10 ng/ml[47]. While interpreting results it should be kept in mind that higher BMI children can show poor response to stimulation test.Clonidine stimulation test is relatively safe and can be done easily in young children. Another test of glucagon stimulation is relatively safe and can be done safely in infant and young children but requires sampling for 3 hours. Overall clonidine stimulation test stands out as first test in children with suspected GHD except in very young children however recent study from Brazil based on Immunochemiluminescent assay (ICMA) has suggested as cut off of > or = 3 ng/ml to be normal[48].

Role of Sex Steroid Priming :

Sex steroid priming before GHST helps in differentiating between true GHD and CDGP. However over the years there has been debate over utility of priming, as some endocrinologists[49] believe that rise in GH post priming is just transient and levels can be insufficient for normal pubertal growth leading to under diagnosis of GHD in children. Advocates of priming[50] argue that it will increase specificity of GHST and will lead to decrease in false positive cases.ESPE[49] had recommended in 2010 that sex steroid priming should be restricted to boys with tanner stage 1 to 2 and age of >13.5-14 year and in girls with age >11.5-2s year with tanner stage 1-2. Rosenbloom[50] has argued this recommendation and suggested for sex steroid priming in all children of prepubertal and early pubertal age group. He particularly stressed upon priming for children during 4-5 year preceding normal timing of puberty. There are several protocols for priming. One protocol given by lazara and Philip is as follows: for girls, single daily dose of oral micronized Estradiol valerate 1 mg for children < 20 kg and 2 mg for children > 20 kg or ethinyl estradiol at the dose of 40 mcg/m2/day for 2-3 days preceding the GHST and for boys as 100 mg of depot testosterone 7- 10 days before testing.Whereas Williams text book1 suggests

giving 100 mg of depot testosterone 3 days before testing in boys and 5 mg of conjugated estrogens orally on the night before and the morning of the test, or 50 to 100 µg/day of ethinyl estradiol for 3 consecutive days before testing in girls.

MRI sella is indicated once diagnosis of GHD is made on provocative testing to rule out any associated developmental abnormalities such as optic nerve hypoplasia or dysgenesis of the corpus callosum and the identification of tumours in pituitary-hypothalamic area. Most common abnormal findings in MRI sella in GHD are presence of either an ectopic posterior pituitary gland or a hypoplastic anterior pituitary gland in association with a hypoplastic or absent pituitary stalk. However in most cases of GHD, MRI sella is normal. Once the diagnosis of GHD is made other pituitary hormone deficiency should be also looked for.

If despite extensive investigation including GHST, no etiology can be identifies then default diagnosis would be idiopathic short stature which is defined as height less than -2 SDS without evidence of any disease after thorough investigation.These children are GH sufficient and are of normal birth weight. These children will require long term follow up to look for growth velocity and appropriate management. Definition of idiopathic short stature also includes children with familial short stature and CDGP.

Table 8 — *Growth hormone stimulations test*

Agent	Mechanism	Procedure	Sampling	Remarks
Clonidine[65,66]	Probably acts through stimulation of GHRH	Clonidine tab 0.15 mg/m² orally	0, 30, 60, 90, 120 min	Watch for hypotension. Children becomes sleepy. Child should be preferably in lying down position during the test, observe subject for at least 2 hours after the test.
Glucagon[67-69]	Causes hyperglycemia leading to increase insulin release and secondary hypoglycemia	30 mcg/kg of SC or IM glucagon max up to 1 mg	- 30, 0, 30, 60, 90, 120, 150, 180	Can have nausea, cramps, delayed hypoglycemia
Insulin[66,67]	Hypoglycemia leading to increase GH response by decreasing SS and increasing alpha adrenergic response	0.10 – 0.15 U/kg IV	-30, 0, 15, 30, 45, 60, 90, 120	Hypoglycemia is a prerequisite for the test to be valid and for same blood glucose must drop by at least 50% from basal or < 40 mg/dl
Levodopa[69,76]	Increase GH secretion by dopaminergic and alpha adrenergic pathway	Oral, < 15 kg - 125 mg, 15 - 30 – 250 mg, > 30 kg- 500 mg	0, 30, 60, 90, 120	Side effects- nausea, vomiting, vertigo
GHRH-arginine test[70,77]	GHRH directly stimulates pituitary for GH secretion whereas arginine causes decrease in somatostatin leading to robust response of pituitary to combined test	1 mcg/kg IV GHRH at 0 min and 0.5g/kg of arginine from time 0 to 30 min (max 40 g)	0, 15, 30, 45, 60, 90, 120	GHRH not available in India

GHRH=growth hormone releasing hormone, GH=growth hormone, SC=subcutaneous, IM=intramuscular, SS=somatostatin

Summary :

Shortness of stature can lead to impaired quality of life. Importance of timely evaluation of stature cannot be overemphasized. Moreover, if diagnosed and treated late, potential gain in height despite treatment becomes low.

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Review Article

Optimal management of Hypothyroidism

Rajesh Khadgawat[1]

Hypothyroidism was the first of the endocrine disease treated by replacement of the deficient hormone with extracts of animal thyroid glands. The development of more purified and synthetic thyroid hormone preparations have made it possible to mimic the function of thyroid gland with thyroid hormone replacement. The treatment of hypothyroidism with synthetic thyroxine is quite safe and well tolerated by most of the patients and can be continued for prolonged periods without a need to bring about many changes in dosage. This review article looks into the practical aspects of management of hypothyroidism.

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Key words **: Hypothyroidism, Thyroxine, TSH, Thyroid gland.**

Hypothyroidism is one of the most prevalent endocrine disorder. The manifestations of the condition can vary from subtle to overt. Most of the manifestations respond well to appropriate replacement of thyroxine.

Pharmacology of Thyroxine :

Thyroxine is available in India in the form of tablets (four to five pharmaceutical brands) of varying strengths from 25 to 200 ug with 100 ug is the most widely used and easily available strength. Tri-iodothyronine (T3) tablets are not available in most of the cities and no parenteral preparation has been marketed in India. Thyroxine tablet seems to be stable if stored properly at room temperature with long shelf life but may lose potency if exposed to moisture, light or air. About 60-80% of the administered dose is absorbed relatively slowly (in comparison to triiodothyronine, which is rapidly absorbed), primarily from proximal small intestine, jejunum. Presence of food has been found to be associated with 30-40% reduction in thyroxine absorption. Ideally, thyroxine should be taken on empty stomach in morning as a single dose and any caloric intake should be avoided for next 30 minutes. Although half life of thyroxine is about 7 days, it is better to take the tablet at the same time every day, to improve compliance.

Initiation of Treatment :

The goal of treatment of a patient suffering from hypothyroidism is to achieve euthyroid state and normalize thyroid function. The initial starting dose of thyroxine depends on patient's age, presence of coronary artery disease and arrhythmias. Thyroxine can be started with full replacement dose (1.6-1.7 ug/kg body weight) in case of a healthy young or middle aged individual with no history of coronary artery disease[1]. In case of elderly persons and patients with history of coronary artery disease, replacement should be started with lower dose. The starting dose may be 25-50 ug/day with increment of not more than 12.5-25 ug. Patients should be clearly explained about possibility of aggravation of symptoms of coronary artery disease, especially chest pain. In case if patient develops chest pain on starting or increasing the dose, it may be decreased up to 50% and cardiac evaluation should be done before increasing the dose further.

Monitoring of Therapy :

Monitoring of adequacy of thyroxine therapy can easily be done by measurement of serum TSH levels. Samples for serum TSH can be collected at any time of the day, irrespective of food intake (fasting is not required) but morning samples are better. Patient should be instructed to take morning replacement dose only after sample collection. The first re-evaluation visit after commencement of treatment should not be before 6-8 weeks. Doses of thyroxine can be increased or decreased based on serum TSH levels. The target serum TSH level for primary hypothyroidism is between 1-3 mU/L. Suppression of serum TSH less than 0.1 mU/L should be avoided as it is associated with higher risk of side effects especially of atrial fibrillation in elderly and increased bone loss in postmenopausal women. Dose changes of 25 ug/day are usually adequate for most of the patients. If serum TSH levels are still high, dose may be increased by 25 ug/day. After 6 months of therapy, the dose should be reassessed as restoration of euthyroidism increases the metabolic clearance of thyroxine.

Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi 110029
[1]MD, DM, Professor and Corresponding author

The dose which was adequate during early phase of therapy may not be adequate when patient is euthyroid because of increased clearance of thyroxine. Once serum TSH comes in target range, monitoring may be less frequent (once in 3 months) for first year and if dose of thyroxine is stable for one year, monitoring frequency may be done once in 6 months or may be once in a year. Adequacy of thyroxine therapy can never be judged on the basis of improvement in clinical symptoms. No change in dose should be done on the basis of persistence of symptoms or disappearance of symptoms.

Central Hypothyroidism :

The most common cause of central hypothyroidism is pituitary adenoma[2]. Isolated secondary hypothyroidism is very rare. Central hypothyroidism is suspected when serum T4 level is low with normal or inappropriately elevated serum TSH level (inappropriate to decreased level of serum T4). Once central hypothyroidism is suspected, it is most important to evaluate other hormones of pituitary, especially pituitary-adrenal axis. The most critical step before starting thyroxine is to rule out hypoadrenalism[3]. Patient with both hypothyroidism and hypoadrenalism may have symptoms of hypothyroidism only but may develop symptoms of hypoadrenalism once thyroxine is started as metabolic clearance of cortisol is reduced in case of hypothyroidism and at times, may lead to acute adrenal crisis. The initiation of thyroxine therapy is similar to primary hypothyroidism but monitoring of therapy is done with serum T4 levels (total or free), not with serum TSH levels. The target level of serum T4 is middle to upper normal range. Pituitary imaging is also required in these cases to rule out any surgically treatable lesion.

Serum Total T4 or Serum free T4 : Which is Better ?

Measurement of serum total T4 and serum free T4 will provide similar information. The measurement of serum total T4 is much easier than that of serum free T4. Measurement of serum free T4 is cumbersome and difficult as this is an assay requiring high precision because we are measuring a hormone in very low concentration in blood. Measurement of serum free T4 is more useful than serum total T4 in conditions only where thyroxine binding globulin (TBG) levels are altered like in pregnancy, when TBG levels are increased[4]. This could be the case in cases of severe illness also where TBG levels are reduced. The congenital deficiency of TBG is a rare condition and its prevalence in India is very low (0.04%, 1 in 2500)[5]. In all non-stressed and non-pregnant individuals, measurement of serum total T4 is as good as serum free T4 and much easier.

What to Do if Patient Forgets to Take Tablet ?

The half life of thyroxine is about 7 days. If some one forgets to take the dose for one or two days in a month, it will not make much effect on serum TSH level. If it is not taken for more than a week in a month, serum TSH level may be affected. If a patient forgets to take the dose in the morning, he or she can take same dose whenever the patient (afternoon or evening) and avoid food intake for next half an hour. If one day dose is completely missed, double dose can be taken next day morning. If a patient forgets to take the medicine for two days, the patient can take triple dose on the next morning without any concern. In case of no dose for more than 3 days, dose should not be increased by three times to compensate for the missed doses.

Duration of Treatment :

Hypothyroidism in majority of patients is permanent, requiring life long therapy. In patients with transient hypothyroidism secondary to sub-acute and postpartum thyroiditis, therapy may be discontinued once hypothyroid phase is over. However, these patients are at higher risk for developing permanent hypothyroidism in future and should be followed up regularly. Once diagnosis of primary hypothyroidism is confirmed biochemically, requirement of life long therapy should be clearly explained to the patient before starting the treatment.

Response to Treatment :

The response to treatment in case of a severely hypothyroid patient is excellent. The increased diuresis is the initial response followed by increase in pulse rate, pulse pressure, appetite and general sense of well being. The changes in skin and hair may take few months to disappear. The serum T4 levels come to normal range within 4-6 weeks while normalization of serum TSH may require few more weeks while complete clinical resolution may require 3-6 months.

Conditions Affecting Requirement of Thyroxine :

Thyroid hormone requirement is altered in many conditions. Any disease of proximal intestine mucosa will affect the absorption of thyroxine like celiac disease and also after jejuno-ileal bypass surgery and small bowel resection. Impaired gastric acid secretion as in atrophic gastritis is also known to reduce absorption[6]. Thyroxine can be adsorbed to co-administered drugs like cholestyramine, sucralfate, aluminium hydroxide, calcium carbonate, ferrous sulfate, lovastatin or various resins, decreasing its absorption and thereby increasing requirement. Similarly, increased requirement has also been found in patients taking medication which induces cytochrome P450 enzyme (CYP3A4) in liver like rifampicin, phenytoin, carbamazepine and sertaline. Estrogen, as used in hormone replacement therapy for postmenopausal women, is also known to increase requirement. Amiodarone increases thyroxine requirement by blocking the peripheral conversion of T4 to T3. Soy protein and soya flavones have been observed to interfere directly with thyroid hormone action[7]. Aging is associated with decreased requirement of thyroxine as clearance of thyroxine is reduced[8]. Similarly, androgen therapy in women (for carcinoma breast) is also known to reduce requirement of thyroxine (Table 1).

Table 1 — *Conditions that alter thyroxine requirements*

(A) Conditions associated with increased thyroxine requirements :
• Gastrointestinal disorders
Mucosal diseases of small bowel
Jejuno-ileal bypass surgery
Small bowel resection
Diabetic diarrhoea
Atrophic gastritis
• Pregnancy
• Interaction with drugs
• Drugs that interfere with absorption – cholestyramine, sucralfate, aluminium hydroxide, calcium carbonate, ferrous sulfate, lovastatin
• Drugs that increase the cytochrome P450 enzyme rifampicin, phenytoin, carbamazepine sertaline, estrogen
• Drugs that block conversion of T4 to T3 – Amiodarone
(B) Conditions associated with decreased thyroxine requirements :
- Aging – 65 years and older
- Androgen therapy in women

Adverse Effects of Thyroxine :

Thyroxine replacement is considered as very safe without much immediate side effects. Allergic reaction to dye used in manufacturing of tablets has been rarely reported. Most of the adverse effects of thyroxine therapy are effects of over replacement. Administration of excessive doses of thyroxine have been found to be associated with accelerated bone loss[9], especially in postmenopausal women[10], increase in cardiac wall thickness and contractility and increases the risk of atrial fibrillation in case of elderly patients.

Dosage in Patients Receiving Thyroxine Without Clear Diagnosis :

It is not uncommon in clinical practice to come across a situation where thyroxine was started on clinical presumption of diagnosis of hypothyroidism without prior thyroid function test or started even in cases of normal serum TSH levels or mild subclinical hypothyroidism. It is very crucial to decide about the future therapy. As primary hypothyroidism is a life long disease, every effort should be made to be certain of diagnosis. The initial serum TSH level report will be very informative, if available. Serum TSH levels more than 20 mU/L at any time during therapy is consistent with diagnosis of primary hypothyroidism. If thyroxine was started with normal or mildly elevated serum TSH levels, the dose of thyroxine may be decreased to half and reassessed after 4-6 weeks. If serum TSH is still normal, thyroxine can be stopped altogether and reassessment after 4-6 weeks will clear the diagnosis. If decreasing thyroxine dose to half increases serum TSH more than 10 mU/L, then the patient should be treated as a case of hypothyroidism.

Patients with Persistent Hypothyroid Symptoms Despite Normalization of Thyroid Function Test :

In some patients with severe hypothyroidism, symptoms of hypothyroidism may persist even when serum TSH has been normalized. Clinical improvement may lag behind biochemical improvement by few months. Reassurance of patient is the most helpful tool in such cases. Excessive thyroxine dose may be one of the causes. This may also happen when monitoring is done with serum T4 and not with serum TSH. If symptoms persist for few more months even after normalization of serum TSH, other causes of these symptoms should be ruled out.

Persistently High Serum TSH Levels :

Persistence of high serum TSH even after adequate duration of treatment is also not uncommon. Poor compliance to treatment is the most common cause. Failure to take thyroxine more than a week in a month may result in high serum TSH. Interference by another co-administered drug (as discussed) should also be suspected. Changing of pharmaceutical brand may also result in elevated serum TSH as bio-availability of all brands may not be the same. If high serum TSH persists even after 3-6 months of regular therapy of adequate doses, possibility of malabsorption should also be ruled out, especially celiac disease[11]. In rare cases, thyroid hormone resistance may be the cause.

Subclinical Hypothyroidism :

One of the most common clinical conditions, in practice, is mild elevation of serum TSH (5-15 mU/L) with normal serum T4 levels[12]. This condition is also known as mild hypothyroidism, early thyroid failure or preclinical hypothyroidism. It represents either early onset of hypothyroidism or variation in thyroid hormone parameters. In the most carefully controlled studies, one or another of the parameter has returned to normal in about 25-50% of patients. The most important decision in these patients to start thyroxine depends upon the likelihood of develop-

ment of overt hypothyroidism. The factors which predispose to development of overt hypothyroidism are progressive increase in levels of serum TSH (over 3-6 months), presence of goiter, high levels of thyroid peroxidase (TPO) antibodies[13] and family history of hypothyroidism. Patients with subclinical hypothyroidism receiving amiodarone or lithium are also at high risk of developing hypothyroidism. Once decision of starting thyroxine has been taken, the initial dose is usually 25-50 ug/day. The target range of serum TSH and frequency of serum TSH estimation is similar to primary hypothyroidism.

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Review Article

Artificial sweeteners — clinical perspective

Puja Dutta[1], Geetu Gupta[2], Rajiv Singla[3], Viny Kantroo[4], Dipanjan Bandyopadhyay[5], Deep Dutta[6], Saptarshi Bhattacharya[7]

Artificial sweeteners (AS) are substances with intense sweetening properties that can be added in small quantities to various foods to enhance its flavour without adding any extra calories. AS has always been under scrutiny and there are various controversies about health risks posed by its consumption. The commonly approved and available AS include saccharin, aspartame, sucralose, neotame and acesulfame potassium. Some natural derivatives like steviolglycosides and sugar alcohols have also been used as sweetening agents. The toxicity profile of these agents has been thoroughly studied and scrutinized and is generally considered safe by various national and international food regulatory authorities. However, the recent clinical trials have shown inconsistent results on weight gain and metabolic benefitwith regular consumption of AS. The current review will focus on effects of AS on clinical parameters like weight gain andglycaemic control and other metabolic risk factors. The safety of usage of AS in setting of pregnancy will also be analysed.

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***Key words* : Artificial Sweetener, Diabetes, Obesity.**

Artificial sweeteners (AS) are known by several names, which include low-calorie sweeteners, high intensity sweeteners, non-nutritive sweeteners, sugar substitutes, etc. AS have a higher intensity of sweetness per gram than caloric sweeteners such as sucrose, corn syrups, and fruit juice concentrates[1]. As a caloric sweetener replacement, they are added in smaller quantities; and provide no or few calories. AS may assist in weight management, control of diabetes and prevention of dental caries[2]. There are other sugar substitutes like sugar alcohols or polyols that produces around 2 kcal/g; because they are not fully absorbed from the gut, polyols are less available for energy metabolism. Taken as a whole, AS are mostly not metabolized in the body and so, are generally considered safe for consumption. AS usage throughout the world, is evaluated by governing bodies; these include the Food and Drug Administration (FDA) of the United States and expert scientific committees such as the Scientific Committee on Food (SCF) of the European Commission, the Joint Expert Committee of Food Additions (JECFA) of the United Nations Food and Agricultural Organization (FAO) and the World Health Organization (WHO). In India, the usage of AS is governed by Food Safety and Standards Authority of India (FSSAI). The FSSAI has approved five AS: saccharin, aspartame, acesulfame potassium, sucralose and neotame. Stevia is also approved in India.

Department of Endocrinology, Max Superspeciality Hospital, Patparganj, New Delhi 110092
[1]MSc, Senior Nutritionist
[2]MSc, Ph D, Senior Nutritionist, Department of Nutrition, Kalpavrisksh Healthcare, Dwarka, New Delhi 110078
[3]MD, DM, Senior Consultant, Department of Endocrinology, Kalpavriksh Healthcare, Dwarka, New Delhi 110078
[4]DNB, Consultant, Department of Pulmonary Medicine, Apollo Hospital, Noida, 201301
[5]MD, Professor & Head, Department of Internal Medicine, North Bengal Medical College, Siliguri 734011
[6]MD, DM, Senior Consultant, Department of Endocrinology, Venkateshwar Hospitals, Dwarka, New Delhi, 110075
[7]MD, DM, Senior Consultant and Corresponding author

Types of Artificial Sweeteners :

(a) Saccharin — Saccharin exceeds the sweetness of sugar by 200 to 700 times. It provides no energy because it is not metabolized by humans[3]. In March 1975, a Canadian study found that male rats experienced increased rates of bladder cancer after consuming high doses of saccharin[4]. Reports however stated that the amount of saccharin rats were eating was the equivalent of a person drinking 800 diet sodas a day. Other studies done during that period also raised doubts about association of high dose saccharin usage to bladder cancer. As a result, from 1981 until 2000, products containing saccharin required warning labels in the USA. The requirement was reversed after the US National Toxicology Program at the National Institute of Environmental Health Sciences found fault with the data and removed saccharin from the list of suspected human carcinogens[5].

(b) Aspartame — It is 160 to 220 times sweeter than sucrose. This sweetener does provide energy; however, because of the intense sweetness of aspartame, a minute amount needs to be added. So, the amount of energy derived is negligible. Foods that contain aspartame are contraindicated for those suffering from phenylketonuria[6]. A

comprehensive review of the safety of aspartame that covered previous publications as well as new information, supported its safety and negated claims of aspartame's association with a range of health problems including brain tumors[7]. The SCF also concluded that current intakes in European countries are well below the acceptable daily intake (ADI) set by JECFA and SCF (40 mg/kg body weight/day) and that aspartame is not a carcinogen and also is not associated with neurobehavioral disorders.8 Currently,aspartame is approved for use in over 100 nations.

(c) Neotame — It has a sweetness potency of approximately 7,000 to 13,000 times than sucrose. It is partially absorbed in the small intestine, rapidly metabolized by sterase, and excreted in urine and faeces. The label for products with neotame do not need to alert phenylketonurics. Neotame consumption at 100 times the ADI in animals did not produce neurotoxic or behavioural or reproductive toxicity effects. In human studies, there were no significant treatment effects of neotame ingestion compared to controls[9].

(d) Sucralose — It is 600 times sweeter than sucrose; it provides no calories as it is poorly absorbed (range 11% to 27%) and is excreted unchanged in the faeces. If at all any sucralose is absorbed, it is excreted unchanged through urine. FDA concluded from a review of more than 110 studies in human beings and animals that sucralose did not pose carcinogenic, reproductive, or neurologic risk to human beings[10].

(e) Acesulfame potassium — It is approximately 200 times sweeter than sucrose. Pharmacokinetic studies show that 95% of the consumed sweetener is excreted unchanged in the urine and does not provide any energy. Consumption of acesulfame-K does not influence intake of potassium[11]. It was evaluated for safety by JECFA in 1983[12,13]. The European Commission's SCF re-evaluated it and supported its safety but recommended an ADI at 9 mg/kg of body weight/day[14]. The amount of acesulfame-K added to food products is very small because of its intense sweetening power and it is often used in combination with other AS.

Acceptable Daily Intake :

The concept of ADI was introduced in 1961 by JECFA. ADI is expressed in mg of additive per kg of body weight and it is the amount of the substance if consumed on a daily basis over a lifetime will not result in any adverse effects. Based on results from animal toxicology studies the no-observed-effect level (NOEL) for a particular AS is determined. NOEL is divided by 100 to determine the ADI for a food additive, a 100-fold safety factor to avoid any possible side effects in humans[3]. If estimated daily intake (EDI) exceeds the ADI, there may be limitations on the use of the sweetener. For sweeteners, testing may be augmented to address specific end points like neurotoxicity testing and effects on humans with relevant conditions like effects on glucose homeostasis in those with diabetes. A recent evaluation of AS intake worldwide revealed that intake of AS are well below acceptable levels[15].

Artificial Sweeteners: Effect on Clinical Parameters :

AS are generally believed to be safe from toxicity point of view. As they hardly provide any calories, they have also long been considered beneficial for those with diabetes and where weight gain is a concern. But over the last decade, new data has emerged that has challenged the notion of metabolic safety of AS.

Risk of Developing Diabetes :

The Health Professionals Follow-Up Study, a prospective cohort study of 40,389 healthy men,concluded that sugar sweetened beverages (SSB) clearly increased the risk of type 2 diabetes. Intake of artificially sweetened beverages (ASB) was shown to be associated with type 2 diabetes in the age-adjusted analysis (HR: 1.91) but failed to show any association in the multivariate-adjusted analysis (HR: 1.09)[16]. The Manhattan study,in which 2019 participants free of diabetes were on longitudinal follow up, showed that consumption of diet soda was associated with risk of incident diabetes. The association depended on BMI at the time of diet assessment though a further sub-analysis in overweight or obese subjects revealed that the association persisted irrespective of BMI in those groups[17]. The Women's Health Initiative (WHI), analysis of a cohort of 64,850 women, revealed that ASB consumption was associated with a higher risk of diabetes with an HR of 1.21 comparing ASB consumption of =2 serving/day to never or <3 serving/month. The study concluded that, consumption of SSBincreased the risk of diabetes by 43% where as ASB intake was associated with a 21% increased risk[18]. Other studies[19-21], including two meta-analysis[22,23], also suggest that although less compared to sugar and SSB, there is an increased chance of developing diabetes with regular AS consumption particularly in obese individuals. One possible explanation behind the association between AS intake and risk of diabetes in observational studies is reverse causation bias, which relates to the fact that obese individuals are more likely to consume AS. Alteration in gut flora induced by AS has been proposed as a mechanism to induce glucose intolerance. The glucose intolerance induced in mice by AS was corrected by addition of antibiotics[24].

Risk of Obesity :

Although AS were designed to restrict calories and promote weight loss, the findings in observational and interventional studies have not been encouraging. Several large epidemiological studies have shown that regular consumption of AS is associated with weight gain[25-28]. Consensus from interventional studies suggest that AS do not help to reduce weight when used alone[29,30]. A review of AS usage in children also showed epidemiological link between weight gain and consumption of AS[30]. In the Baltimore Longitudinal Study of Aging, after a10-year mean follow up, AS users had (0.80 kg/m^2) higher BMI, (2.6 cm) larger waist circumference and (36.7%) higher prevalence of abdominal obesity compared to non-users[31].

Regular users of AS are hypothesized to have increased desire for high calorie and sweet foods. AS may interfere with the physiological mechanisms that enable to predict the caloric content of food based on sweet taste causing overconsumption of calories. Sucralose was shown to modulate physiological parameters involved in normal body weight regulation by activation of sweet taste receptor in the brain that might potentially affect appetite regulation by providing an inaccurate signal regarding the actual levels of extracellular glucose in the brain[32,33]. Thesweet-taste receptors in the intestine could interact with AS and stimulate glucagon-like peptide 1 (GLP-1) secretion which in turn leads to insulin release from pancreas. Rise in insulin secretion can increase appetite and result in weight gain[34].

Impact on Glycemic Control in Diabetics :

Diabetics are advised to restrict simple carbohydrates like glucose, sucrose, fructose, etc. Foods containing AS provide alternatechoices, making possible increased variety, compliance to prescribed meal plans and in some cases, improved psychological well-being.A multicenter, double-blind, placebo-controlled, three month randomized study, in diabetics, in whichsucralose was administered at a dose approximately three times the maximum estimated daily intake, showed no adverse effect on any measure of blood glucose control in individuals with type 2 diabetes[35]. A review on AS also concluded that it did not adversely impact glycemic control in individuals with diabetes[36]. A recent meta-analysis concluded that consumption of AS did not increase plasma glucose concentrations. The glycemic impact of AS intake did not vary according to the type of AS, but did differ to some extent depending on age, body weight, and status of diabetes[37]. In another study, it was demonstrated that intake of diet soda before a glucose load increased GLP-1 secretion in non-diabetic controls and in those with type 1 diabetes but not in type 2 diabetic subjects. Glucose-dependent insulinotropic polypeptide (GIP) and peptide YY (PYY) secretion were not altered by consumption of diet soda. The clinical significance of this finding is however not yet clear[38]. The current understanding is that AS does not impact glycaemic status in diabetic subjects. Whether it has any additional and indirect action on incretins and other gut hormones in diabetic subjects needs further evaluation.

AS Usage in Childhood :

As a means to help curtail the obesity epidemic, dietary changes to prevent weight gain in children and adolescents have been encouraged. A key question is whether replacement of sugar-sweetened products with those containing AS in children is truly beneficial. The general trend is that AS may reduce total caloric intake when consumed between meals, but when consumed with meals, children may compensate for low-calorie snacks or drinks by increasing meal-associated calories. A review of AS usage in children also showed epidemiological link between weight gain and consumption of AS[30]. Another interesting aspect that draws attention on AS usage among children is addiction to sweet foods. Though most addiction research examines more common drugs of abuse, such as alcohol, cocaine, morphine, and nicotine, various studies have drawn parallels between drug seeking behavior and food seeking behavior. This has led some to believe that sugar and other sweet substances could become physiologically addictive[39]. Majority of pediatric epidemiologic studies have found a positive correlation between weight gain and ASB intake. Blum *et al* examined ASB consumption and BMI Z-scores in 164 elementary school-aged children. This longitudinal study found that increased diet soda consumption was positively correlated with follow-up BMI Z-score after two years[40]. Comparable results were found by Berkey *et al*, who examined the relationship between BMI and diet soda consumption in over 10,000 children (aged 9 to 14 years) of Nurses' Health Study II participants over the course of one year[41]. Thus,recent epidemiological and clinical findings question whether recommendations for the use of AS in children is appropriate.

AS Usage in Pregnancy :

Although AS such as aspartame, acesulfame-K, and saccharine are generally considered safe with respect to acute toxicity, the overall safety of regular consumption during pregnancy is still disputed because the outcomes of AS usage on the fetus are not clear. Human studies found that the breakdown products of aspartame cross the placenta[42]. But, consumption of aspartame during pregnancy is not expected to be a concern when staying within the ADI[43]. There is limited research on the safety of acesulfame potassium during pregnancy, but studies have found that this sweetener does cross the placenta. However, these results were reported for concentrations of acesulfame potassium that were substantially greater than typical human exposure[44]. A case-control study also reported that risk of spontaneous abortions in women was not increased in those who consumed saccharin[45]. Some studies do report that high intake of both AS and SS beverages is associated with an increased risk of preterm delivery[46]. The

study involved 59,334 pregnant women and evaluated the association between intake of sucrose-sweetened soft drinks, carbonated or not, and preterm birth (< 37 weeks) infants as the primary endpoint. A high intake of ASB was associated with preterm delivery; the adjusted OR for those drinking >1 serving/d was 1.11 (95% CI: 1.00, 1.24). The trend tests were positive for both SSB & ASB types[46]. Reinforcing this data, a study linked the high intake of ASB with prematurity; the adjusted OR for those who drank > 1 serving/day was 1.11 (95CI = 1.00 - 1.24)[47]. Further studies are needed to reject or confirm these findings. Maternal consumption of AS during pregnancy may also influence infant BMI[48]. Findings illustrated positive associations between intrauterine exposure to ASB and birth size and risk of overweight/obesity at 7 years[49]. Carbonated ASBs were also associated with registry-based asthma and self-reported allergic rhinitis, while early childhood outcomes were related to non-carbonated soft drinks[50]. These results suggest that consumption of ASB during pregnancy may play a role in offspring allergic disease development. Consumption of AS during pregnancy might have a negative effect on the pregnancy outcome in terms of preterm delivery. There are also some doubts about long term outcome in children who had exposure to AS in utero and more data is required before recommendations about routine usage of AS in pregnancy can be advocated.

Conclusion :

Though AS consumption is not associated with toxicity like carcinogenesis, but there are unresolved questions regarding its metabolic safety. At this time, the available data is insufficient to conclusively determine whether the use of ASin beverages and foods reduces weight or prevents diabetes. The evidence reviewed suggests that when used judiciously, AS could facilitate reductions in consumption of calories ascompared to sugar and SSB. But, these theoretical advantages might not translate to expected clinical benefits because of compensatory increase in energy intake from other sources, alterations in gut flora and abnormal response of gut hormones. Further studies are required to ascertain the metabolic safety of these substances.

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Review Article

Dietary approaches in management of Diabetes : current perspectives in India

Lovely Gupta[1], Priti Rishi Lal[2], Deepak Khandelwal[3], Piyush Gupta[4]

Optimal management of diabetes leading to good metabolic control, prevention of complications and concomitant avoidance of hypoglycaemia is a key to successful management of this disorder. With the available nutritional management guidelines, and diversity of current dietary approaches in India, the need for comprehensive, patient-centered and flexible national nutritional guideline is still felt.The review focuses on various dietary approaches used for diabetes management in India.

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***Key* words : Diabetes, India, diet, carbohydrate, macronutrients.**

Indian Council of Medical Research (ICMR) defined diabetes mellitus as a metabolic-cum-vascular syndrome of multiple etiologies characterized by chronic hyperglycemia, disturbances of carbohydrate, fat and protein metabolism and causing defects in insulin secretion, insulin action or both[1]. It is mandatory for the people with diabetes to maintain a discipline and balance between nutritional management, physical activity and medical treatment as a part of diabetes self-management[2,3].Good glycaemic control early in the disease results in lower frequency of chronic diabetes complications, which in turn reduces the healthcare cost[4].

Dietary Approaches in Management :

Various nutritional guidelines and target glycemic goals for diabetes are given by Diabetes Control and Complications Trial (DCCT), Stockholm Diabetes Study in type 1 diabetes, UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, International Diabetic Federation (IDF), American DiabetesAssociation (ADA), The British Diabetes Association, European Association for the Study of Diabetes (EASD), American Heart Association (AHA), Canadian Diabetes Association, Indian Diabetes Prevention Program (IDPP), ICMR, Research Society for the Study of Diabetes in India (RSSDI), etc aiming to improve health outcomes[5-13].

[1]M Sc, Nutitionist, Department of Food and Nutrition, Lady Irwin College, University of Delhi, New Delhi 110001
[2]M Sc, Ph D, Department of Food and Nutrition, Lady Irwin College, University of Delhi, New Delhi 110001
[3]MD, DM, Senior Consultant, Department of Endocrinology, Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi 110026
[3]MD, Consultant, Department of Paediatrics, Maharaja Agrasen Hospital, New Delhi 110026

There are no disease-specific nutrition guidelines for youth with T1DM. For the nutritional management of blood glucose levels, optimising the role of macronutrients, monitoring carbohydrate intake (carbohydrate majorly affects postprandial blood glucose levels) and balancing carbohydrate intake with insulin levels is recommended to be central to all the dietary approaches[14]. Similarly, for type 2 diabetes management, all the guidelines emphasize towards initial therapy with lifestyle intervention such as healthy balanced diet with energy balance, primary prevention of overweight, and obesity, quality and quantity dietary carbohydrate, protein, fat and micronutrient intake and other specific nutrition recommendations, using exchange lists for meal planning with optimum food choices to meet recommended dietary allowances (RDA)and carbohydrate counting with adequate physical activity[15]. It will ensure normal body weight, decrease insulin resistance and achievement of optimum growth and development. Thereafter the treatment therapy moves towards the addition of medications, transition to new regimens when target glycemic goals are not achieved or sustained and addition of insulin therapy for the people who are not able to meet the patient-specific individualised target goals[5,7,16,17]. There is no clear evidence of benefit from vitamin or mineral supplements for the patients who have no underlying deficiencies. The RDAs of micronutrients should be met from natural food sources through intake of a balanced diet[18].

A meta-analysis was conducted by Schwingshackl *et al*, 2018 on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. It has shown that various dietary approaches such as low-fat, Vegetarian, Mediterranean, high-protein, moderate-carbohydrate, low-carbohydrate, control, low GI/GL and Palaeolithic diets significantly reduce HbA1c (-0.82 to -0.47% reduction) and fasting glucose (-1.61 to -1.00 mmol/l reduction) compared to a control diet[19].

Anderson *et al*, 1993 used nutrition interventions such a healthy food choices, exchange systems, carbohydrate counting, total available glucose and behavior management approaches coupled with intensive insulin therapy for the attainment of normoglycemia in the Diabetes Control and Complications Trial (DCCT)[20]. Contextually, Ortiz *et al*, 2014 showed that basic carbohydrate counting, glycemic index, and glycemic load are important tools for patients to master for their blood glucose control[21]. Furthermore, reviews conducted by Jain, 2014 and Smart *et al*, 2014 highlighted that optimal glycemic control in T1DM requires a balance of insulin therapy with diet and exercise with greater flexibility in lifestyle[22,23]. Various nutritional approaches have been implemented and evaluated for improvement of glycemic control among people with diabetes (summarised in table)[16,24-40].

Nutritional Recommendations at Clinical Level :

While planning various dietary approaches, dieticians and health care professionals distribute the respective patient-centered recommended calories into the macronutrients by counting the amount of carbohydrates, proteins and fats per day as per disease condition. In diabetes, the carbohydrates are evidenced to dominantly cause postprandial rise in blood glucose levels while proteins and fats cause a prolonged blood glucose rise by 3-4 hours after food ingestion, and frequently, a relative insulin resistance[41]. The micronutrients are later calculated to meet RDAs and specific physiological needs.

Conclusion :

There are diverse nutritional approaches being practiced in India. There is no tailor-made approach to diabetes. Nutritional recommendations are timely modified with respect to patient-centered factors, challenges and disease complications. Matching the dietary composition with the blood glucose levels and insulin dose adjustments can help us achieve the optimum goals of nutrition therapy among people with diabetes.

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(Continued on page 77)

Review Article

Major risks indicators for diabetic kidney disease

Sameer Aggarwal[1]

Diabetic nephropathy, which is defined as elevated urine albumin excretion or reduced glomerular filtration rate or both, is a serious complication that occurs in 20–40% of all diabetic patients. There is marked racial/ethnic difference besides international difference in the epidemiology of diabetic nephropathy. Hyperglycemia is a well-known risk factor for diabetic kidney disease, in addition to other risk factors such as male sex, obesity, hypertension, chronic inflammation, dyslipidemia, and some genetic loci and polymorphisms in specific genes. Management of its modifiable risk factors might help in reducing its incidence in the near future.

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Key words **: Diabetic kidney disease, Risk factors, Albuminuria**

Risks for diabetic kidney disease have focused on those associated with loss of renal function, particularly glomerular filtration rate (GFR). Loss of renal function includes many aspects other than GFR. A number of comorbidities result from, or are exacerbated by, damage to the kidney: hypertension, anemia, disordered bone and mineral metabolism, dyslipidemia, and inflammation. These co-morbidities may contribute to further kidney dam-age, as well as to cardiovascular disease (CVD). The latter issue is of particular concern because most people with diabetes who develop CKD will die of CVD rather than reach ESRD[1]. Because diabetes and CKD pose a high risk of mortality and morbidity, the pur-pose of this review is to review major risks indicators. Identification of risks allows for development of improved strategies for detection, intervention, and novel therapeutic approaches.

Predictors of Kidney Disease in Early Diabetes :

Renal Hemodynamics :

Genetic predisposition undoubtedly contributes to the development of kidney disease in diabetes. In addition, early renal functional changes have also been associated with subsequent kidney disease. Glomerular hyperfiltration, a higher than normal GFR, has long been recognized in recent-onset type-1 or -2 diabetes[2,3]. In observational studies of persons with type-1 diabetes, those with higher GFR levels have been described as being more likely to develop micro- or macroalbuminuria many years later[4,5]. In classic physiologic studies, diabetic rats were found to have high GFR owing to increased glomerular perfusion and pressure[6]. Intraglomerular hypertension was shown to play a key role in hyperfiltration and subsequent renal injury in diabetes or with high-protein diets in other experimental models[7]. Furthermore, feeding diabetic rats a high-protein diet greatly exacerbated renal injury and loss of function[8]. Conversely, a low-protein diet protected the kidney even in the setting of continued hyperglycemia[8]. Another important observation from this study was that the diabetic rats exhibited greater sensitivity to the renal hemodynamic effects of dietary protein than the normal rats[8]. These data suggested that interactions between the defining feature of diabetes, hyperglycemia, and dietary protein produce an augmented glomerular hyper filtration response and, consequently, kidney damage.

In human physiologic studies, those with either type-1 or -2 diabetes had an augmented glomerular hyperfiltration response that was greatly increased beyond that of nondiabetic individuals when a mixed amino acid (AA) solution designed to resemble a protein meal was infused intravenously[9]. These data suggested that hyperglycemia was necessary but not sufficient to produce glomerular hyperfiltration in diabetes. Human studies were consistent with the animal models in demonstrating greater sensitivity to renal hemo¬dynamic effects of dietary protein,

Hormonal responses to protein feeding or an AA infusion could be responsible for increasing renal perfusion and GFR.

Individuals with diabetes have enhanced sensitivity to AAs as well as to glucagon, another stimulus that raises GFR. Although glucagon and prostaglandins do not appear to be primary causes of AA-induced renal hemodynamic changes in diabetes, they could produce glomerular hyperfiltration under other conditions, such as more severe hyperglycemia.

Cellular Mechanisms :

AAs could directly injure cells and participate in processes induced by high levels of glucose. The mesangial cell culture model was chosen because it is a key cell involved in regulation of renal hemodynamics, as well as the profibrotic and proliferative response to injury in diabetes. Increased AAs, alone or in combination with a high glucose level, induced mesangial cell proliferation and fibrosis[10]. In addition, the profibrotic response was mediated by increased expression and activation of transforming growth factor-f3. Because of the remarkable similarities between effects of glucose and AAs on mesangial cells, a common metabolic pathway could be responsible. Advanced glycation end products (AGEs) are formed by nonenzymatic glycation of free amino groups, followed by a complex series of sequential glycation and oxidation reactions. Although previous research has focused on hyperglycemia as the main causal factor, increased availability of free amino groups could also initiate these reactions. If so, then cell signaling pathways associated with AGEs should also be activated and participate in the injury responses. In a series of experiments, it was found that AGE formation was increased by the AA condition, and that the combination condition of AA/High glucose (HG) appeared to produce an even greater amount of AGEs[11]. Preventing AGE formation with aminoguanidine blocked the profibrotic mesangiul cell response. Cell signaling pathways associated with AGEs, oxidative stress, and activation of protein kinase C and mitogen-activated protein kinases extracellular signal-related kinases were increased by the AA, HG, and AA/HG conditions. Their causal roles in the profibrotic response were confirmed by specific inhibition of these processes. These observations provide insight into cellular mechanisms of injury induced by AAs and a potential explanation for increased sensitivity of the diabetic kidney to damage resulting from high dietary protein. Furthermore, AGEs are associated with widespread vascular damage and consumption of foods with increased amounts of AGE-modified proteins increase circulating AGEs and inflammatory markers in diabetic subjects[12]. AA-induced injury could be produced at sites other than the kidney, and that the arterial circulation may be particularly vulnerable. In support of this, a study of persons with type-1 diabetes and early CKD (on average stage 2) showed that a modest reduction of dietary protein decreased the combined end point of death and ESRD[13]. Deaths were predominantly owing to CVD and were decreased as much, or more, than cases of ESRD. Thus, limiting exposure to dietary protein and, consequently, increased levels of AAs, may protect against CVD as well as CKD.

Kidney Disease as a Window to the Circulation :

Development of kidney disease in diabetes reflects processes operative at distant sites that have a major impact on risks of adverse outcomes. Albuminuria is the earliest clinical indicator of CKD in diabetes. However, albuminuria also increases risk of CVD events and death independent of traditional risk factors[14]. Although this relationship is particularly apparent in diabetes", albuminuria also appears to increase CVD risk in other groups, including those with essential hypertension and the general population[15]. In a study of persons undergoing elective coronary angiography, there was a direct correlation between albuminuria levels and severity of coronary artery disease[16]. This relationship was most pronounced in the subset of individuals with type-2 dia¬betes. Importantly, the levels of albuminuria that correlated with coronary artery disease were largely below the traditional threshold for defining microalbuminuria (albumin-to-creatinine ratio <30 mg/g). This concept is also supported by data from the Heart Outcomes Prevention Evaluation (HOPE) study that showed that risk of major CVD events in high-risk patients, with and without diabetes, increases at levels of albuminuria far below the traditional threshold for microalbuminuria[17]. Therefore, elevated levels of albuminuria defined by predicting progression of kidney disease may be higher than those that predict clinically important CVD.

As for most CVD risk factors, the relationship to CKD appears to be continuous. Risk of major CVD events increases even further as albuminuria progresses to clinical albuminuria (albumin-to-creatinine ratio >300 mg/g) or overt proteinuria (dipstick-positive, protein-to-creatinine ratio >500 mg/g). Risks for strokes and coronary events are amplified afact, most people with CKD will die-of CVD and not reach ESRD. People with both diabetes and decreased GFR are at especially high risk of cardiac death[19].

The strong influence of kidney disease on CVD is likely to be multifactorial. There are several possible explanations: vascular disease expressed at the level of the kidney reflects greater severity; persons with CKD have a greater burden of traditional risk factors including diabetes; CKD produces nontraditional risk factors[20]. It is important to recognize that these possibilities are not mutually exclusive. Endothelial injury, a key component of the atherosclerotic process, occurs in the glomerular microcirculation and in the circulation at large. Albuminuria is believed to be an excellent marker of this process. In persons with known coronary heart disease, defined by a previous myocardial infarction, albuminuria correlated directly with the transvascular escape rate of albumin[21]. Even in apparently healthy persons, increased levels of albuminuria are associated with endothelial dysfunction, as determined by impaired flow-associated dilation of the brachial artery[22]. Thus, albuminuria can be considered an indicator of endothelial injury in the kidney as well as at distant sites in the circulation.

[1]MD, DM, Senior Consultant & Head, Department of Endocrinology & Metabolism, Apex Plus Superspeciality Hospital, Rohtak 124001 and Corresponding author

Persons with type-2 diabetes and albuminuria have a particularly high risk of CVD. A seminal question is whether or not reduction of albuminuria predicts improved risk status. In secondary analyses of the Reduction in Endpoints in Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial, lowering albuminuria was associated with reduced risk of renal and cardiovascular events[23]. This has been interpreted to mean that albuminuria should be a therapeutic target in type 2 diabetes. However, a limitation of this interpretation is that those who were responsive to treatment with the angiotensin receptor blocker may have had less severe disease. Nevertheless, the hypothesis that albuminuria should be a therapeutic target is an important one worthy of prospective testing. Other important questions are embedded in this hypothesis: Do albuminuria-reducing treatments other than angiotensin receptor blockers improve outcomes? Do treatments without an effect on albuminuria improve outcomes?

In summary, indicators of CKD in diabetes, albuminuria, and decreased GFR, reflect damage to the kidney that predicts a broad spectrum of adverse outcomes in multiple vascular target organs.

Conclusions :

Risks for diabetic kidney disease have traditionally focused on those associated with loss of renal function, particularly GFR. Loss of renal function also encompasses many aspects other than GFR: hypertension, anemia, disordered bone, and mineral metabo¬lism, dyslipidemia, and inflammation, among others. Many of these disturbances are more prevalent, occur' earlier, and are more severe in diabetes than in other forms of CKD. Furthermore, they may contribute to further kidney damage, as well as to CVD. The latter issue is of particular concern because most people with diabetes who develop CKD will die of CVD rather than reach ESRD. Predictors of early kidney disease, focusing on renal hemodynamic disturbances produced by diabetes and nutritional influences (excess dietary protein), were discussed. Evidence for a direct effect of dietary protein, acting through increased AAs, to induce mesangial cell injury was also presented. Finally, the concept that indicators of CKD, albuminuria, and decreased GFR, reflect widespread circulatory disease was reviewed.

Development of kidney disease in diabetes heralds a number of adverse outcomes.

An understanding of major risks indicators should facilitate future research designed to elucidate basic mechanisms of disease at one end of the spectrum, whereas improving design of clinical trials on the other. Indeed, identification of major risks indicators is a critical component of translational research, the bench-to-bedside paradigm.

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Review Article

Hypothyroidism in elderly patients

Abhinav Nair[1], Sachin Chittawar[2], Deepak Khandelwal[3]

Hypothyroidism is more common in the elderly population, partly because of the increased prevalence of autoimmune thyroiditis. Accurate diagnosis of the disorder is complicated due to a multitude of factors. Management in the elderly depends on factors with respect to the metabolism of thyroid hormone and is also affected bydrug interactions. Over zealous treatment can lead to fatal arrhythmias and loss of bone density which has to be taken care of while treating the patient. In patients of mild or subclinical hypothyroidism where treatments were aimed at normalizing thyroid functions, the results have been conflicting. [*J Indian Med Assoc* 2018; **116:** 78-81]

***Key words* : Hypothyroidism, India, Elderly, Treatment.**

There has been a paradigm shift in the recent decades with respect to the health of elderly population. Hypothyroidism is a disease that increases in both prevalence and incidence among the elderly. The challenge for the clinician being that the clinical manifestations of hypothyroidism may be less obvious in the setting of somatic complaints and establishing a diagnosis is cumbersome due to a relative lack of referable complaints, other confounding findings related to comorbid conditionsassociated with ageing process, upward rise in TSH levels that may occur with increasing age and changes in thyroid hormone levels that may be related to non-thyroidal illness.

Prevalence / Burden :

Hypothyroidism is commoner in elderly population groups, in comparison to youngerindividuals, and is higher in the female gender attributable probably to the increasing incidence and prevalence of autoimmune thyroiditis, it has also been seen that the incidence of hypothyroidism increases with increasing age[1,2]. As with other diseases, incidence and prevalence estimations have fluctuated probably because varied population groups were studied, as well as due to variety of criteria used in defining the disorder. In a survey done in the past, which employed the calculated free thyroxine index, it was found that about 2.3% patients had the required criteria to diagnose hypothyroidism[2]. Other community based studies of healthy adult population showed that 7 to 14%of elderly population had serum TSH levels above the normal upper limit of reference values[3,4]. In some studies, prevalence of hypothyroidism in community population and elderly hospitalized group have been found to be comparable. The Third National Health and Nutrition Examination Survey (NHANES III) showed that a significantly higher number of women in age group of 50-59 and 60-69 met the benchmark for diagnosis of hypothyroidism(clinical and subclinical) in comparison to men who were in similar age brackets. A study assessing elderly(geriatric) patients on medical treatment reported that about 17% of males and 15% of females had not been diagnosed with hypothyroidism previously[5]. A study of older adults reported that every one out of 10 women and one out of 50 men were on thyroid hormone supplementation which had been on prescription[6], and within this population,about 12% of the women and 29% of the men were found taking thyroid hormone for reasons deemed inappropriate. It is quite certain that the estimations of the prevalence and incidence of hypothyroidism in the elderly population need to consider the ever-increasing evidence that normal TSH values and curves of distribution seem to take a shift to the higher side with increasing ages. Study of TSH levels with respect to age and anti-thyroid antibody titers measured as part of therecent NHANES study reported that 12% of subjects over 80 years without evidence of underlying autoimmune thyroiditis had TSH levels higher than 4.5 mIU/L[7]. With respect to the role of dietary iodine, most studies have inclined towards the notion that iodine deficiency appears to have a protective role against the development of hypothyroidism in the elderly[8,9]. A study done recently in North India showed that a significantly higher proportion of women *versus* men (15.86% *versus* 5.02%) and elderly vs. younger (13.11% *versus* 7.53%) adults were diagnosed with hypothyroidism. Thus, females and elderly were found to be having a significant link with developing hypothyroidism, autoimmune mechanisms probably appeared to play a causative role in a large proportion of patients[10]. A recent study in South India showed that thyroid function disorders are common in elderly; affecting about 14% of study population, overt hypothyroidism being the most common thyroid disorder (5.81%), followed by subclinical hypothyroidism (5.54%). Abnormalities in thyroid function were shown to have an increasing incidence with age in both genders[11].

[1]MBBS, Senior Resident, Department of Medicine, Gandhi Medical College (GMC) and Hamidia Hospital, Bhopal 462001
[2]MD, DM, Associate Professor, Division of Endocrinology, Gandhi Medical College (GMC) and Hamidia Hospital, Bhopal 462001
[3]MD, DM Senior Consultant, Department of Endocrinology, Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi 110026

Physiology and Thyroid Function Tests :

There are various implications of understanding the physiological changes in levels of TSH with increasing age. Regarding physiology, the aging thyroid gland is characterized by several microscopic changes.

Microscopic Changes : Prominent changes include arise in the inter-follicular connective tissue. The size of the follicles decreases and so does the colloid content (the matrix in which the hormone is stored). With increasing age, these areas begin to lack colloid content, while in other areas the follicles are composed of pale colloid, that indicate a decreased store of thyroid. The epithelium of the glands undergo atrophy with flattening and reduction in size of the lining cells. The bulk weight of the gland itself decreases, with a slight increase in volume. Basal utilization of oxygen per unit surface area reduces which is similar to that in patients with hypothyroidism. Therefore, it can be said that the researchers who postulated that hypothyroidism is probably a normal result of the aging process were correct in their own way, and some even suggested that following the administration of thyroid hormone to older patients, their BMR(basal metabolic rate) showed a rise.

There have been many studies that have investigated the role of thyroid gland and its function in aging. Recent studies also show a rise in serum TSH levels with age, independent of the presence of antithyroid antibody[6]. While contrasting studies have demonstrated a decrease in serum TSH in older population1[2,13], the relationship between TSH values and age seems to depend on the nature of thyroid pathology. In patients with Hashimoto's thyroiditis, there is a tendency of TSH to increase with rising age[14,15], whereas in populations with iodine deficiency where the thyroid pathology includes nodularity and increase in thyroid autonomy with age, a fall in TSH levels are suggested with increasing age16. With regards tofree T3 levels, most studies have demonstrated an age-dependent decline, while free T4 levels remain quiteunaltered[12,13] while rT3 levels show a rise with increasing age. It is interesting to note however that interpreting thyroid functions in elderly is complex due to the presence of chronic illnesses and consumption of multiple drugs by the patient[17]. There is now evidence that raised TSH levels are associated with longer life, a study reported that serum TSH levels were significantly higher in centenarians (mean age=98 years) as compared to controls[18]. Most other studies have also depicted higher TSH levels (mean age=85 years) and low to low-normal FT4 levels (mean age=78 years) tohave an association with a longer period of survival in elderly[19,20]. The hypothesis to the association of a higher TSH level with longevity may be attributable to a reduced bioactivity of thyroid hormone,which causes a lower basal metabolic rate and potentially serves to be an adaptation to prevent catabolism in the elderly[20].

Etiology In Elderly :

Autoimmune thyroiditis is the commonest cause of hypothyroidism among the elderly, as it is in the younger population[21], this was established in a study of patients attending an endocrinology clinic where 57% of patients above the age of 55 years were diagnosed as having autoimmune thyroiditis while 32% carried a diagnosis of postsurgical hypothyroidism and 12% had a diagnosis of post-radioiodine hypothyroidism[21]. Only about 2% of patients in this population presented with evidence of secondary hypothyroidism.

Clinical Features :

Classical Symptoms : Easy fatiguability, generalized weakness, weight gain, anorexia, dry skin, pedal edema, goitre, constipation, sleep apnoea, cold intolerance, hairloss, confusion, lassitude, depression.

Classical Signs : Facial puffiness, dry skin, bradycardia, myopathy, recession of eyebrows and frontal hair, cerebellar signs, effusions, delayed ankle jerk relaxation.

Two signs found in more than 50% elderly patients [22]:

- Fatigue.
- Weakness.

Four signs found less frequently in elderly compared to young :

- Chilliness, Parasthesias, Weight gain, Cramps.

Clinical presentation that heighten suspicion in older age group compared to young —

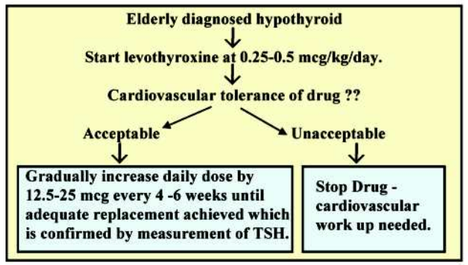
- Congestive cardiac failure(restrictive cardiomyopathy)
- Fecal impaction(due to retarded stool movement through bowel)
- Macrocytic anemia
- Unexplained elevations in plasma cholesterol or triglyceride levels
- Vague arthritic complaints
- Psychiatric complaints- depression, myxedema madness.Rare- syncope, seizures .
- Physical findings evident in hypothyroid elderly individuals may include bradycardia, diastolic hypertension, pallor, dry skin, coarse hair, hoarseness, dysarthria, delayed relaxation of deep tendon reflexes, and mental status changes.
- Other features suggestive-Thyroidectomy scar, impaired cerebellar function, history of radioiodine therapy, goitre, family history of thyroid disease.

Morbidity :

Medical complications of hypothyroidism which are

severe are also more common in the elderly, as evidenced by the fact that almost all patients presenting with myxedema coma are elderly, and those patients in this age group maybe at a higher risk for developing complications related to surgery (perioperative and intraoperative). A comparative study of patients with unrecognized hypothyroidism with controls matched for age, sex, and operative procedure showed an increased rate of heart failure, intraoperative hypotension and postoperative gastrointestinal and neuropsychiatric complications in hypothyroid patients[23].

Treatment :



A recent survey of the members of the American Thyroid Association confirmed that this general strategy was adopted in practice[24]. A trial showed that elderly patients devoid of underlying cardiac illnesses could be started safely on full replacement doses of thyroxine(1.6mcg/kg) without side effects[25]. Following a change in dosage of thyroid hormone, TSH levels should be measured every four to six weeks and most experts recommend a target level of normal TSH range in the elderly[26], Whereas an estimated 39% ofATA members suggest targeting a TSH range of 0.5-2.0 mIU/L while treating younger population with hypothyroidism, a comparable number suggested that they were generally more liberal with regards to their approach to older patients, targeting TSH ranges of 1.0-4.0 mIU/L.While an optimal target would be to supplement thyroid hormone to a level which corrects the deficiency completely, patients with coronary heart disease may be unable to tolerate those doses of thyroxine.One study of patients with known coronary artery disease and primary hypothyroidism reported that precipitation of angina symptoms limited titration of thyroxine in two-thirds of cases, while precipitation of hypothyroid symptoms limited titration of anti-anginal agents in one-third of cases, and despite adding propranolol at maximally tolerated doses, about 46% of the patients suggested that the control of their angina and hypothyroid symptoms was only fair to poor[27]. A study proposed that lean body mass was probably a better predictor of replacement doses each day rather than age or weight[28], while another study reported that majority of the age-dependent differences in thyroxine requirements noted might be due to the effects of chronic illnesses, because a significantly lower mean daily replacement dosing was seen in older patients being treated for other chronic medical disorders[29]. A study tracking the variations in thyroxine requirements of older patients over time based upon the cause of their primary hypothyroidism showed that daily replacement doses increased in patients who initially presented with autoimmune thyroiditis or postsurgical hypothyroidism, reduced in patients who initially presented with post-ablative hypothyroidism, and was unchanged in patients who initially presented with subclinical hypothyroidism or drug-induced hypothyroidism[30]. In situations where cognitive or functional impairment may make it difficult for patients to comply with daily administration of thyroxine, alternative dosing schedules may be considered. Polypharmacy is a major issue with many drugs known to interfere in metabolism of thyroxine like calcium carbonate,ferrous sulfate, sucralfate, aluminum hydroxide, cholestyramine, colestipol, raloxifene and estrogen replacement therapy. Long-term administration of phenytoin, carbamazepine, phenobarbital, or rifampin in the setting of treated primary hypothyroidism typically increases metabolism of thyroxine and increase in the dose of thyroxine required to provide optimal replacement. Overtreatment with excessive doses of thyroxine may be associated with significant morbidity in the elderly. Palpitations, anxiety, tremulousness, irritability, insomnia, heat intolerance, hyperdefecation, and weight loss may be precipitated or exacerbated by iatrogenic thyrotoxicosis.A study that tracked bone mineral density changes in women treated with thyroxine documented greater mean rates of bone mineral loss in the lumbar spine of women with suppressed TSH levels[31]. With respect to mild/subclinical hypothyroidism, the consensus recommendations of the American Thyroid Association and the American Association of Clinical Endocrinologists advise treatment of subclinical hypothyroidism involving a TSH level greater than 10.0 mIU/L. In patients with lesser elevations of TSH, however, clinical judgment is critical in deciding whether to treat or monitor[32]. Consequently, a recent consensus statement issued by an expert panel recommended that cases of mild hypothyroidism presenting with TSH levels ranging from 4.5-10.0 mIU/L be treated on a provisional basis, with continuation of therapy predicated on clear evidence of improvement in symptoms consistent with thyroid hormone deficiency[33].

Conclusion :

Hypothyroidism in the elderly population is a common condition which requires a keen clinical suspicion for diagnosis due to obscuration of many signs and symptoms compared to the younger population. The management of hypothyroidism in elderly is challenging due to physiological changes with age, cardiac, bone problems and differences in treatment responses to levothyroxine. Therefore a clinician needs to be alert and aware of the issues related to hypothyroidism in elderly.

Conflict of interests : None

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Case Report

A case of early morning abnormal behavior and refractory epilepsy

Deepak Khandelwal[1], Deep Dutta[2], Joshita Gupta[3]

Insulinomas are rare neuroendocrine tumors of pancreatic islet cells that retain the ability to produce and secrete inappropriately high insulin. The clinical symptoms of insulinoma are the subsequent to development of hypoglycemia. We herein present a case of one patient who had been symptomatic for 6 years with symptoms of early morning abnormal behavior and refractory epilepsy, which eventually was diagnosed as a case of Insulinoma and could be cured after successful removal of lesion. All patients with unexplained abnormal behavior and seizure disorder should have blood glucose level checked during the episode. [*J Indian Med Assoc* 2018; **116**: 82-3]

Key words **: Epilepsy, hypoglycemia, insulinoma**

Case Report

A 54 year old lady was admitted for evaluation of refractory epilepsy. She had been symptomatic since last 6 years, when she started having episodes of abnormal behavior early in the morning. Her husband with whom she lived reported that her abnormal behaviors were in multiple forms like repeatedly cleaning the house at same place or many times she used to be confused and was reacting inappropriately to situations. During these episodes minimal sweating was noticed by her husband, otherwise she didn't have any other complaint during the episodes. Also, she could not remember these episodes. Earlier frequency of these episodes was approximately one episode once a week. Other than early morning frequent episodes, day time episodes were observed when she used to have fast for religious reasons. She was seen by a neurologist and was started on antiepileptic drugs after a diagnosis of seizure disorder. Her electroencephalography (EEG) and magnetic resonance imaging (MRI) of brain was normal. Because of no response even with multiple antiepileptics, she was referred to psychiatrist and was treated with antidepressant and antipsychotic drugs with no response. Frequency and severity of these episodes worsened gradually. Over the years, her husband had noted that the symptoms could be promptly relieved by giving the patient morning tea, which was a custom in the house to have with jaggery. Two years before hospitalization, she also started having episodes of generalized tonic-clonic seizures followed by unconsciousness almost daily early in the morning. Subsequently patient had consultation with many neurologists, with frequent change of antiepileptics and psychiatric medication. She was labeled as a case of refractory epilepsy and was hospitalized for evaluation. During one of episodes in hospital her blood sugar was found to be low. Subsequently, multiple episodes of hypoglycemia could be documented with corresponding inappropriately high insulin and c peptide levels. She had no personal or family history of diabetes mellitus, and was not taking oral hypoglycemics or insulin. Her episodes of hypoglycemia and corresponding laboratory values are summarized in Table 1.

Finally, a diagnosis of hyperinsulinemic hypoglycemia was made and for localization she underwent multiphasic computed tomography (CT) and MRI of abdomen, in which arterial enhancing lesion in body of pancreas was found. Meantime she was started on frequent complex carbohydrate based diet with two additional night time feedings, which failed to control her early morning and nocturnal hypoglycemic episodes. After that she was started on 5 mg prednisolone at bed time in view of inappropriately low cortisol response at many times during hypoglycemic episodes (Table 1), which is well described in literature in patients with Insulinoma[1,2]. After that her hypoglycemic episodes could be controlled and she didn't have any further episodes of hypoglycemia in next six weeks. All antiepileptics' were discontinued, with no recurrence of seizures. She was also detected to have hypertension and was controlled on amlodepine 10 mg/day and enalapril 5 mg/day preoperatively. Work up for secondary causes of hypertension, including for pheochromocytoma was negative. Subsequently patient was operated and 1 x 1 cm lesion was identified in body of pancreas during intraoperative palpation, and was also confirmed in intraoperative ultrasonography and successfully removed. Histopathology confirmed the lesion to be an insulinoma. Postoperative period was uneventful; she was rapidly tapered off steroids after that. After 10 months of surgery, the patient was symptom free, and has normal blood glucose values.

Discussion

Insulinomas are rare neuroendocrine tumors of pancreatic islet cells that retain the ability to produce and secrete insulin. The clinical symptoms of insulinoma are the subsequent development of symptoms of hypoglycemia. The leading symptoms establishing the diagnosis of endogenous hyperinsulinism comprise the Whipple's triad. This includes : (1) symptoms of neuroglycopenia, (2) documented hypoglycemia (plasma glucose levels <50 mg/dl), and (3) symptoms relief (often within 5-10 minutes) following glucose administration[3]. Clinical manifestations of an insulinoma can mimic central nervous system disorders, like epilepsy and psychiatric disturbances[4]. Dizon AN *et al*, reported that before the confirmation of diagnosis of insulinoma, 39% of the cases are diagnosed as epilepsy, 12% of the cases are treated with antiepileptic drugs, and 89% of patients with insulinoma are confused while 64% of them have personality changes and abnormal behaviors5. Chronic hypoglycemic symptoms associated with hypoglycemia appear in patients with insulinoma and in many diabetic patients treated with excess insulin, and these symptoms are similar to schizophrenia, depression, and dementia.

Our patient typically had episodes of abnormal behavior and confusions in early morning before breakfast, and later had more severe episodes associated with generalized tonic clonic seizures. However typical history was overlooked and only after six years, correct diagnosis was made. In summary, the symptoms caused by hypoglycemia show great variability and hence the difficulty in the diagnosis. Higher brain dysfunction might become permanent if the diagnosis of insulinoma is delayed. Atypical seizure or abnormal behaviors, especially in the fasting state, are sometimes observed as hypoglycemic symptoms of insulinoma. Clinicians should take the history of symptoms carefully. Insulinoma should be considered in patients with no reason for having drug-resistant epilepsy, and blood sugar measurement should be a routine investigation at time of witnessed seizures. Another important point that our case highlights that transient hypothalamic- pituitary- adrenal axis suppression can be there in patients with insulinoma with its recovery after successful surgery[1,2]. In fact, our patient very well responded to 5 mg/day prednisolone daily at bed time, which is likely a good therapeutic option in these patients till they are waiting for surgery to take care for life threatening hypoglycemias. There are very few previous reports of short term successful use of steroids in patients with insulinomas[1,6]. Suzuki K *et al*[7], have also reported one patient of insulinoma presenting with stereotypical abnormal behavior of nocturnal paroxysmal arousals, including wild laughing and walking around early in the morning and complete amelioration of these symptoms on prednisolone 10 mg/day at bed time after the diagnosis.

Table 1 — *Episodes of documented hypoglycemia in hospital and corresponding laboratory values*

BG (mg/dl) Glucometer value	BG (mg/dl) Laboratory value	Serum Insulin (μU/ml)	Serum C-peptide (ng/ml)	Serum cortisol (μg/dl)	Plasma ACTH (pg/ml)	Serum GH (ng/ml)
39	42	33.44	7.08	10.81	Not done	0.224
48	51	47.34	7.53	4.58	21.47	0.223
38	40	23.33	6.82	13.72	7.99	0.061

BG- Blood glucose; ACTH-Adrenocorticotropic hormone; GH- Growth hormone

Conflict of interests : None

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Department of Endocrinology & Diabetes, Maharaja Agrasen Hospital, Punjabi Bagh, Delhi 110026
[1]MD, DM, Senior Consultant and Corresponding author
[2]MD, DM, Senior Consultant, Department of Endocrinology, Diabetology & Metabolic Disorders, Venkateshwar Hospitals, New Delhi 110075
[3]MBBS, Department of Family Medicine, Maharaja Agrasen Hospital, Punjabi Bagh, Delhi 110026

Brief Communication

The gustatory hexad

Dharini Krishnan[1], Madhumitha Krishnan[2], Atul Dhingra[3], Sanjay Kalra[4]

The Gustatory Hexad builds upon earlier nutrition and culinary models such as the nutritional triad, culinary pentad and degustatory pentad. Inspired by Ayurveda, it lists six tastes (rasas) which must be satisfied during the course of a day's meals. These tastes-sweet, sour, salt, pungent, bitter and astringent- serve as a checklist to help ensure nutritional adequacy, especially micronutrient balance, and culinary acceptance. Adherence to the Gustatory Hexad allows for healthy dining and digestion, which in turn promote optimal health, and healthful outcomes. Understanding of this concept may help plan therapeutic interventions for gustatory autonomic neuropathy.

[*J Indian Med Assoc* 2018; **116**: 84 & 88]

Key words **: Autonomic neuropathy, culinary diabetology, diet, medical nutrition therapy, obesity, overweight, underweight.**

Medical nutrition therapy (MNT) is an integral part of diabetes and metabolic care[1]. Modern definitions emphasize that MNT is much more than a simple product. MNT encompasses both individualized diets, and the process by which this information is shared. MNT is delivered by registered nutrition professionals, who aim to provide person-specific meal plans, to ensure optimal health[2,3].

It is understood, however, that diabetes care should be an interprofessional and interdisciplinary effort MNT, similarly, needs collaboration between various professionals, including dietetics and nutrition, endocrinology and diabetology, as well as culinary science. A comprehensive MNT should include inputs from all these diabetes care providers. This allows MNT to be crafted and communicated in a person specific manner. This approach is similar to the patient-centred philosophy followed while planning pharmacological therapy[4].

The Degustatory Pentad :

Modern models provide guidance regarding the goals of integrated MNT, and the strategies necessary to achieve these. These concepts, in turn, facilitate optimal choice of nutritional therapy, and ensure concordance with other forms of glucose lowering treatment.

These models provide an overview of nutritional, culinary and degustatory aspects of MNT. The degustatory pentad is inspired by the philosophy of Vietnamese cuisine. This lists the five senses-vision, olfaction, taste, touch and hearing-which should be stimulated by food[5].

The Gustatory Hexad :

Ayurveda, one of the traditional Indian schools of medicine, goes a step further. It explains that food consists of six tastes primarily. For a person to remain healthy, all these six tastes should be had on a daily basis through food[6]. These six tastes, or 'rasas' are listed, with examples, in Table 1. We term this the Gustatory Hexad (Fig 1). An understanding of the components of food that contains these rasas helps one prepare a meal plan based on the individualistic requirement, which includes various food groups, satisfies the palate, and ensures a balanced diet with adequate micronutrient content. The gustatory hexad, as we term it, is relevant not only to home cooked food and fine dining cuisine, but also to MNT.

Table 1 — *The gustatory hexad*

Taste	Sanskrit	Examples
Sweet	Madhura	Sugar, jaggery
Sour	Amla	Lime, citrus
Salt	Lavana	Salt, rock salt
Pungent	Katu	Pepper, chilly
Bitter	Tikta	Bitter gourd, neem
Astringent	Kashaya	Black tea, butter milk

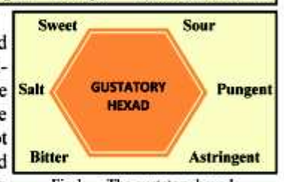

Fig 1 — The gustatory hexad

Clinical Relevance :

The gustatory hexad should be studied in conjunction with culinary triads and pentads that have been published earlier. This model focuses detail on a relevant aspect of MNT, and serves as a checklist for providers. It helps improve the quality of care provided through MNT, by en-

(Continued on page 88)

[1]MSc, Ph D, Director, DV Living Sciences Private Limited, Chennai 600004
[2]MD, Pediatric Ayurvedic Consultant, Bangalore
[3]MD, DM, Consultant, Department of Endocrinology, Bansal Hospital, Sri Ganganagar, Rajasthan 335001
[4]MD, DM, Senior Consultant, Department of Endocrinology, Bharti Hospital, Karnal 132001

Commentary

Type 2 Diabetes reversal in India : Is a low carbohydrate diet practical and sustainable ?

Rahul Rosha[1], Saptarshi Bhattacharya[2], Sameer Aggarwal[3], Rajiv Singla[4]

The root cause of type 2 diabetes mellitus (T2DM) is carbohydrate intolerance and insulin resistance. From a scientific perspective, our body doesn't need carbohydrates. While carbohydrate restriction per se can cut the cycle of glucose and insulin surges, it is "nutritional ketosis" that puts metabolic syndrome into reversal. Although variable from person to person, to get blood ketones above 1 mmol (optimal ketosis), it is typically required that one consumes less than 50 grams of carbohydrates/day. The typical recommendation is starting at 30 grams/day of carbs – a level that most people can consume and remain in nutritional ketosis, and at the same time affording us a wider range of food choices. In the context of a well-formulated Ketogenic diet, this level is safe, sustainable and satisfying. Once keto-adapted, depending on your metabolism and goals, one can incorporate slow release carbohydrate such as root vegetables, legumes etc.

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Key words **: T2DM, Nutritional ketosis.**

The root cause of T2DM is the combination of insulin resistance and carbohydrate intolerance. Carbohydrate intolerance occurs when more carbohydrates are consumed than one's tolerance level, which causes blood glucose to go high and stay higher for longer. Insulin is released in response to increases in blood glucose to help the glucose move to insulin sensitive tissues, where it can be used for energy or stored. Insulin resistance means that cells are resistant to the signal of insulin and stop responding - so most of the glucose stays in blood, leaving a situation with chronic high blood glucose. Chronic high blood glucose is the primary marker of T2DM and prediabetes, and to diagnose these conditions the glycosylated hemoglobin (A1c) test is used.

Widely held belief is that these diseases are caused by being overweight, eating too much fat, or not exercising enough - but because diabetes is by definition a disease of high blood glucose, the real underlying cause are conditions resulting in high blood glucose - the combination of excess carbohydrate intake along with carbohydrate intolerance or insulin resistance. While weight gain is associated with diabetes, it is an effect, not a cause - which is why there are diabetic patients who are never overweight. While exercise can help improve blood glucose, the lack of it is not the primary cause of high blood glucose.

In the last decade, oxidative stress and inflammation have been identified as key underlying causes of T2DM[1,2,3]. This is potentially transformative, because while T2DM has been known to be caused by insulin resistance, despite 50 years of intense research, no one has been able to pinpoint the root cause(s) of insulin resistance. Now we know that ketones at the normal levels characteristic of nutritional ketosis reduce oxidative stress and inflammation, and these benefits can be traced to the actions of genes we are all born with[4,5]. But without modest levels of circulating ketones, these inborn defences don't function properly. Stating this another way, eating a high carbohydrate diet turns off our defences against oxidative stress and inflammation, and this deactivation in turn contributes to (if not causes) insulin resistance. Furthermore, as noted above, the more dietary carbohydrates we consume, the greater the tide of glucose needing to be disposed of, which tends to further increased insulin resistance. It bears repetition that while carbohydrate restriction per se can cut the cycle of glucose and insulin surges, it is "nutritional ketosis" that reverses the essential pathophysiology of T2DM.

Human body requires many things in order to be healthy: sleep, water, micronutrients such as vitamins and minerals, as well as the macronutrients protein and fat. What it doesn't need, from a scientific perspective, is carbohydrates. This does not mean that blood glucose is unimportant but rather that blood glucose can be well maintained via metabolic processes such as gluconeogenesis without carbohydrates in a keto-adapted human.

While a plate of pasta may well be comfort food, it's

[1]MBA, CEO, Novique Health Pvt Ltd, Pune 411018
[2]MD, DM, Consultant Endocrinology, Max Healthcare, Delhi 110092
[3]MD, DM, Consultant Endocrinology, Apex Plus Superspeciality Hospital, Rohtak 124001
[4]MD, DM, FRCP (Edin), Chief Medical Officer, Novique Health and Consultant Endocrinology, Kalpavriksh Healthcare, Delhi 110078 and Corresponding author

not a power food. Human body will turn that simple carbohydrate into glucose rapidly, which will be burned by brain, muscles and other organs for a quick burst of energy, leaving a sensation of hunger and tiredness soon thereafter. And with underlying T2DM, pre-diabetes, or insulin resistance, body struggles to process the carbohydrate, leaving behind worsening glycemic control. Instead, a meal of grilled chicken and a salad full of healthy fats such as avocados, olives, nuts, cheese and ranch dressing, human body can fuel itself entirely on those nutrients without giving a post-meal glucose spike.

For somebody, who has been eating a typical Indian diet, his/her body is running primarily on carbohydrates. Besides carbohydrates, the average Indian diet also tends to be high in saturated fat, trans-fat (mostly related to widespread use of Vanaspati, a form of hydrogenated vegetable oil), and low in protein, cholesterol, monounsaturated fat (MUFA), and polyunsaturated fat (n-3 PUFA), and fiber[6].

But for somebody, who is facing medical problems stemming from processing carbohydrates, such as T2DM, prediabetes, insulin resistance, or metabolic syndrome, a low-carbohydrate approach can be life changing. As carbohydrates are strategically removed from diet, usually to an initial level of 30g per day, body will begin to run on fat as a fuel, both from ingested exogenous fat as well as endogenous fat from body stores. This adaptive process takes a few weeks to shift (typically 2-6 weeks) from carbohydrate-as-fuel to fat-as-fuel, during which liver will pitch in to produce glucose from protein in a process called gluconeogenesis.

The key to successfully—and sustainably—reducing carbohydrate intake to a level that body can effectively process is to replace those carbohydrate calories with a generous amount of healthy fats (such as olive oil, avocados, butter, and cheese) while consuming a standard, moderate amount of protein (from varied sources including meat, poultry, fish, eggs and nuts)

What Does the Term "Diabetes Reversal" Mean ?

- This is called "reversal" because most people can maintain blood glucose values below the diabetes range as long as they maintain a ketogenic diet. However, in most cases, if they return to a carbohydrate-rich diet, their diabetes will return. Thus this is a state of reversal, not a cure.
- The term "reversed" is used if average weekly fasting blood glucose values remain below 126 mg/dl, or if HbA1c remains under 6.5% without any diabetes medications other than metformin. Metformin is excluded from this medication list because there is no reason to stop it in most people whose diabetes has been reversed. That's because it has been shown in humans to prevent progression from prediabetes to diabetes, and because it also has been shown in animals to extend life and health.

Can Type 2 Diabetes Be Reversed ?

All of this makes for a nice story, but up until recently it has been pretty much a hypothetical game of connecting dots. What's needed is the evidence that T2DM in humans can be prevented or reversed by withholding dietary carbohydrates to a level that allows nutritional ketosis to occur. Before insulin was discovered and purified in 1920, going back to the time of the Greeks, the only treatment for diabetes was total starvation or severe carbohydrate restriction, but there was no practical dietary strategy that made this a sustainable solution.

The turning point came in 1976, when Bistrian et al reported seven cases of type 2 diabetes reversal for one year using a very low calorie ketogenic diet[7]. Following that, there have been multiple attempts to confirm and extend this pioneering report[8,9,10,11], but all of these clinical studies have used a ketogenic diet for only a few months, followed by a return to diets rich in carbohydrates. Dashti *et al*[12] reported a series of 30 cases of T2DM reversed by a ketogenic diet over 56 weeks, but did not report how many patients were initially enrolled, and they did not report what, if any, medications were taken by these patients.

We have many anecdotes of people with T2DM who have utilised a long-term, well-formulated ketogenic diet to loose excess weight, but more importantly many of them also returned their blood glucose values into the normal range for years without medication[3]. While some would claim that this is merely an effect of weight loss per se, Boden *et al*[14]. demonstrated dramatic improvements in both blood glucose control and insulin sensitivity in just two weeks when a ketogenic diet was eaten to satiety. This is consistent with the observations of Shimazu[4], Newman[5], and Youm[15] showing that modest blood levels of ketones directly regulate genes that protect us from oxidative stress, insulin resistance, and inflammation.

Which brings us back to the question: can type 2 diabetes be reversed? Given the recent discoveries that beta-hydroxybutyrate (ketone body) triggers dramatic reductions in oxidative stress and inflammation, which in turn reduce the root cause of insulin resistance, there is just one remaining question—can a well-formulated ketogenic diet be followed long term? If the answer to this question is yes, then it follows that type 2 diabetes definitely can be reversed.

Making diabetes biomarkers like HbA1c or fasting plasma glucose better for a few months or even a year is good. Doing it while reducing medication use and reducing excess weight is even better. But if these benefits cannot be sustained, it is just another rollercoaster ride that so many people with T2DM have previously experienced. The key piece to this puzzle is sustainability.

Getting real people to substantially change what they eat and continue to do so for years is really hard. Most people with T2DM have been educated to increase their exercise, avoid dietary fats, eat "healthy carbs," and limit calories. Reversing this failed treatment paradigm takes targeted education and coaching, but this process is aided when it delivers positive and self-reinforcing results. Early and sustained success with improved blood glucose control, reduced medication use, and medically significant weight loss creates patient empowerment and positive outcomes.

How Low :

Inducing a state of nutritional ketosis and maintaining it long enough to complete keto adaption requires a conscientious effort to restrict carbohydrates for two or more weeks. The level of carbohydrate restriction required to optimize fat burning and fat loss varies from person to person, but the most consistent effects will be obtained at below 50 grams per day[16].

This is often asked: "Why to recommend starting at 30 grams?" After all, there is no actual physiological need for any amount of carbohydrate in the human diet. The answer is that 30 grams is a level that most people can consume and remain in nutritional ketosis, and at the same time affording us a wider range of food choices. Carbohydrates from nutrient-rich sources like non-starchy vegetables, nuts, seeds, and full fat dairy products provide enhanced variety, texture, and essential minerals like magnesium, potassium, and calcium. This 30 g requirement will change over time based every individual's unique biochemistry and level of carbohydrate tolerance. Most people fall b/w 30-50 grams of required carbohydrates to stay in optimal nutritional ketosis (b/w 1-3 mmol blood ketones).

How Fast to Cut Back ?

The answer is not clearly spelled out by objective research as one would like. Some authorities advocate easing into carbohydrate restriction slowly by cutting back one food category at a time (eg, first sugars and juices, then refined carbs, then starchy vegetables, etc). Others take the "Nike approach" – as in "just do it". To date, no one has done a study with a large group of subjects to see which strategy yields a higher proportion making an effective transition into nutritional ketosis.

What we do know is that it takes a couple of weeks to keto-adapt, and you don't accomplish much towards that goal until you are making substantial amounts of ketones (ie, eating less than 50 grams of carbohydrates for most people). The other concern with easing into a low carb diet is that once you are eating less than the 150 grams of carbohydrates needed to feed brain with glucose, but still more than the 50 grams threshold below which ketosis is dependably operating, the brain's fuel supply becomes pretty tenuous. If there's not enough glucose to meet the brain's 600 calorie daily energy habit, and blood ketones remain below the 0.5 millimolar threshold where they can begin to pitch in, the body's only two options are:

(1) Burn up protein (for gluconeogenesis to fill the gap)
or
(2) Binge on carbohydrates

In our clinical experience, the "Nike" approach is better. Particularly, if enough sodium is consumed and plenty of low carbohydrate vegetables eaten to get enough potassium, your adaption period will be short and relatively symptom-free.

Conflict of Interest :

Authors are associated with Novique Health Pvt Ltd., a start-up working in field of diabetes reversal using very low carbohydrate diet approach and providing continuous remote diabetes care.

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(Continued from page 84)

suring a holistic (and healthy) culinary and nutritional experience.

The MNT provider should be aware of each element of the hexad, its sources, properties and advantages, and its contraindications, if any. The ideal diet, and ideal MNT, should aim to ensure stimulation of sweet, sour, salt, pungent, bitter, and astringent tastes. There may be situations, however, where some rasas are contraindicated (eg; salt in severe hypertension, sweet in diabetes) or not tolerated (eg, pungent and bitter). In these cases, balance can be achieved by changing the proportion of other components of the gustatory hexad.

It is not necessary to include all these gustatory factors in every meal, or every dish. These can be satisfied at any time of the day, through major meals, or snacks, and main courses or side dishes. Appetizers, desserts and digestives can also be used to ensure completeness of the hexad. Sweet and astringent properties, for example, are easily met through desserts and digestives.

Apart from its relevance to routine therapy, the Gustatory Hexad may inform MNT approaches to specific disease conditions. Diabetes and hypertension can be managed by reducing sweet and salty foods, respectively. Persons with obesity may benefit from greater proportion of bitter (or appetite reducing) foods, while those with constipation require astringent rasa.

Summary :

The Gustatory Hexad is a taste-based culinary framework, inspired by Ayurveda. It serves as a checklist to ensure delivery of MNT which is adequate from a nutritional, and appealing from a culinary perspective.

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Commentary

SGLT2-Inhibitors and cardiovascular outcomes : inferences for clinical practice

Saptarshi Bhattacharya[1], Amit K Adhikary[2], Sudipta Mondal[3], Dipanjan Bandyopadhyay[4]

Cardiovascular risk is the keyconsideration in the management of type 2 diabetes mellitus. Evolving evidence suggests possible cardiovascular protection with certain agents of the SGLT2 inhibitors (SGLT2-i) class. It is important to understand the meaning of the available evidence, for the clinical practice setting. This review attempts to interpret the finer aspects of the available evidence, for appropriate translation to practice.

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***Key words* : Type 2 diabetes mellitus, Cardiovascular disease, SGLT 2 inhibitors.**

The present understanding of cardiovascular disease (CVD) in type-2 diabetes mellitus (T2DM) has evolved considerably. Diabetes and CVD are known to share common antecedent factors. The risk of CVD increases progressively across the continuum of dysglycemia, beginning from the pre-diabetic stage. Subclinical CVD is prevalent in 2 out of every 3 patients of diabetes, andis associated with 2-fold greater risk of CV events.1Intensive control of glycemia has notconsistently demonstrated reduction in risk of macrovascular events, orimprovement in survival[2-7]. Aholistic multi-factorial CV risk management is key to improve clinical outcomes. However, CVD still remains the leading cause of mortality in T2DM, accounting for nearly 2 of every 3 deaths[7].

Recent advances from the CV outcome trials of the SGLT2-inhibitors (SGLT2-i) and GLP-1 receptor agonists (GLP1-RAs), has prompted optimism in the management of T2DM from CVD risk perspectice[8-11]. The CVbenefits demonstrated in EMPA-REG OUTCOME, LEADER, SUSTAIN-6, and CANVAS program,haveushereduniqueopportunities forimproving the standards of care. This review attempts to infer the evidence on CV outcomes with the SGLT2-i agents, from a clinical practice perspective.

The Story of 2 CVOTs : CANVAS Program and EMPA-REG OUTCOME —

CANVAS program was a pooled analysis of 2 randomized controlled trials, CANVAS and CANVAS-R[11,12]. The pooled analysis had a hierarchialstatistical assessment plan, as described in Fig 1.

What is the CV benefit : 3P-MACE in CANVAS Program and EMPA-REG OUTCOME ?

The CANVAS program was statisticallydesignedto detectCV safety of canagliflozin, in terms of 'non-inferiority' for 3P-MACE[12]. The analysis did provethe same;further, a significant 14% reduction in the risk of 3P-MACE events was also demonstrated with canagliflozin. As per the statistical analysis plan of CANVAS program, 'superiority' of canagliflozin for 3P-MACE was considered,based on the hazard ratio of 3P-MACE demonstrating upper bound of 95% confidence intervalas <1.0[11,12]. However, the statisticalassessment planofthe CANVAS program did not assume statistical power to detect 'superiority'for 3P-MACE[12]. In thestatistical considerations, a balance between the possibility of false-positive (alpha) error, andthe power of study, should be optimized for maintaining robustness[13]. In the CANVAS program, since the superiority of 3P-MACE was not considered in the hierarchial assessment plan, a greater statistical power should have been required to optimally reduce the chances of falsely positive 3P-MACE results, which was not the case. However, if the statistical-assumptions of the CANVAS program are reconsidered in the hindsight, it remains uncertain whether such a stricter interpretation should prevail. For demonstration of superiority, the left-truncated dataset that excludes the events accrued in CANVAS before Nov 2012should have been more appropriate. This is because the events accrued in CANVAS before Nov 2012, were partially unblinded for safetyassessments[12]. In the CANVAS program, an additional aspect needing further explanation is that the patients receiving diuretic therapy in the background, had demonstrated significantly greater 3P-MACE benefit;this subgroup analysis suggested that background diuretic use

[1]MD, DM, Senior Consultant, Department of Endocrinology, Max Superspeciality Hospital, Patparganj, Delhi 110092 and Corresponding author

[2]MD, Assistant Professor, Department of Medicine, Raiganj Government Medical College, Raiganj 733134

[3]MBBS, Junior Resident, Department of Medicine, North Bengal Medical College, Siliguri 734101

[4]MD, Professor & Head, Department of Medicine, North Bengal Medical College, Siliguri 734101

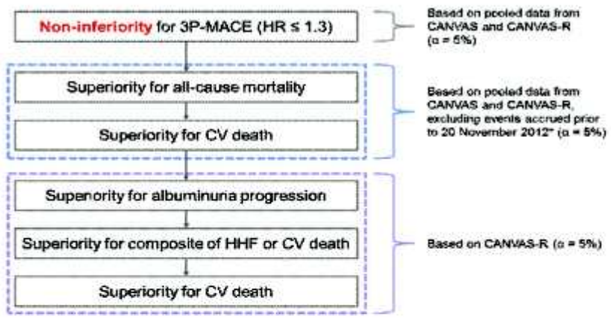

Fig 1— CANVAS Program: Sequential Statistical Analysis Plan

could have considerably influenced the overall CV benefit observed with canagliflozin, with the p value for interaction being <0.001[11]. However, in the EMPA-REG OUTCOME study, such discordant beneficial effect based on the background diuretic use, had not been observed with empagliflozin.8Based on all these considerations, the accurateestimation of 3P-MACE from the left-truncated dataset, using optimized statistical power and alpha-error assumptions, whether canagliflozin would have consistently demonstrated superiority for 3P-MACE, remains uncertain. Overall, the results of the CANVAS program do suggest the possibility ofCV protection with another SGLT2-i agent, in patients of T2D with high CV risk. Based on these observations with their strengths and limitations, the ADA has considered 3P-MACE benefit of canagliflozin as Level C evidence (Conflicting evidence with weight of evidence supporting recommendation).

In the EMPA-REG OUTCOME study, a significant 14% reduction was observed with empagliflozin for 3P-MACE events.8In EMPA-REG OUTCOME as well as in CANVAS program, silent myocardial infarction was excluded from the primary analysis of 3P-MACE[8,11]. Since a precise and timely ascertainment of silent MI is not possible in CVOTs, including silent MI in the primary outcome of 3P-MACE leads to increased uncertainty in the CV safety assessments; hence to maintain robustness of 3P-MACE endpoints, silent MI is generally excluded from primary assessments in CVOTs.

For any therapy, a reduction in all-cause deathis the strongest evidence of benefit; the endpoint of all-cause deathcannot be manipulatedby considering different definitions for specific causes of death.14In terms of all-cause death, empagliflozin demonstrated significant 32% reduction in the EMPA-REG OUTCOME study.8 The mortality benefits of empagliflozin,including all-cause death and CV death, remained consistent even after excluding the 'non-assessable CV deaths' from the analyses[15]. In the CANVAS program, significant reduction in risk of all-cause death or CV death was not observed with canagliflozin, even in those 6,656 patients who had a prior history of CVD[11,28]. Thus, empagliflozin and liraglutide are presently the only 2 antidiabetic agents, which have conclusively proven mortality benefitsin robust studies[8,9].

The overall CV outcomes observed in EMPA-REG OUTCOME, and in the CANVAS program, have been summarized in Table 1.

At what stage of CVD, is the benefit more plausible?

The antidiabetic CVOTs are required to include patients of T2DMwith high CV-risk[18]. The definitions of high CV-risk may vary across the CVOTs.The seminal work of Preiss and colleagues suggested that in patients with diabetes, the presence of underlying CVD would yield a 3.5 to 4.6 fold higher CV event rate[19]. Preiss and colleagues defined underlying CVD based on objective criteria for ascertainingcoronary artery disease, peripheralarterial disease, or cerebrovascular disease. Objective identification included either a prior CV event history or confirmation

Table 1 — *CV Outcomes in EMPA-REG OUTCOME and CANVAS Program. Relative Risk Reductions (dark boxes imply statistically significant reductions)*
This is not a head-to-head comparison

	EMPA-REG OUTCOME	Pooled CANVAS Program
3P-MACE	14% (HR 0.86, 95%CI 0.74-0.99)	14%* (HR 0.86, 95%CI 0.75-0.97)
CV Death	38% (HR 0.62, 95%CI 0.49-0.77)	HR 0.87 (95%CI 0.72-1.06)
All-cause Death	32% (HR 0.68, 95%CI 0.57-0.82)	HR 0.87 (95%CI 0.74-1.01)
Nonfatal MI	HR 0.87 (95%CI 0.7-1.09)	HR 0.85 (95%CI 0.69-1.05)
Nonfatal Stroke	HR 1.24 (95%CI 0.92-1.67)	HR 0.90 (95%CI 0.71-1.15)
HHF	35% (HR 0.65, 95% CI 0.50-0.85)	33% (HR 0.67, 95% CI 0.52-0.87)
HHF or CV Death	34% (HR 0.66, 95%CI 0.55-0.79)	22% (HR 0.78, 95%CI 0.67-0.91)

* Analysis not powered to detect superiority for 3P MACE

through gold-standard assessments, like vascular imaging in asymptomatic or symptomatic patients. Such objective definitionfor underlying CVDensures greaterhomogeneity of underlying CVD risk in the study populations, and has been followed as inclusion criteria in TECOS and EMPA-REG OUTCOME[8,20].

In clinical practice setting, an objective assessment of underlying CVD by vascular imaging is not routinely recommended inasymptomatic patients of T2DM[21]. Silent ischemiais of common occurrence in asymptomatic patients of T2DM, often with significant underlying atherosclerotic obstruction, and may manifest as serious events like silent MI or sudden death.It is known that in diabetes, the underlying atherosclerotic plaques are diffuse, andremain asymptomatic for a longer duration[22]. The Framingham offspring study suggested that 2/3rdof the patients of diabeteshaveunderlying subclinical CVD.1 Further, a post-mortem assessment in patients of diabetes haddemonstrated high-grade coronary atherosclerosis,in 3/4th of the patients who had been asymptomatic; half of the patients having multi-vessel disease. Hence, if the assessment of underlying CVD is based merely on clinical symptoms, one maymiss out on a significantproportion of patients with subclinical CVD, who also have high CV risk. In the CVOTs, if objective assessment for underlying CVD is not considered as the inclusion criterion, enrollment of participants with high CV risk may be maximized by includingthosewith multiple uncontrolled CV risk-factors. CVOTs like LEADER, CANVAS program,and DECLARE TIMI 58 have included patients of high CV risk based on these lines[9,11].

In CANVAS program, 66% of enrolled patients had symptomatic atherosclerotic CVD, whereas 34% had multiple CV risk-factors, without a known history of CVD. In these 34% of study participants, the CVD status was not excluded by vascular imaging[11]. The mean age of the study patients was 63 years,and average duration of diabetes was 14years; hypertension was present in 90% of these patients.11As the CVD status was not excluded through vascular imaging, it would be inappropriate to assume absence of underlying CVD, in these 34% of patients with high CV risk, enrolled in the CANVAS program.

In the CVOTs, the 3P-MACE event rates in placebo groups indicate the background CV risk in the respective study participants. As demonstrated in Fig 2, in the placebo groups across most of the CVOTs, the 3P-MACE event-rateswerecomparable (Fig 2)[8-12,20,24]; this is suggestive of similar background CV-risk in the participants across these CVOTs.Since all the CVOTs include patients with high CV-risk profiles, attempts to extrapolate the beneficial CV outcomes observed in these CVOTs, to patients with lower CV-risk profiles, may befutile.

Trial	High CV Risk: Definition (Established CVD / Presence of CV Risk-factors)	Incidence rate of 3P-MACE Events (Placebo group)
LEADER	Age ≥50 and CHD / Cerebrovascular disease / PVD / CKD stage ≥3 / CHF (NYHA 2-3) **OR** Age ≥60 with ≥1 CV risk-factor (proteinuria, HT and LVH, LVSD or DD, ABPI <0.9)	3.4 per 100 pt-yrs
SUSTAIN-6	Similar to LEADER	4.4 per 100 pt-yrs
SAVOR TIMI-53	Age ≥40, and clinical atherosclerotic event (coronary / cerebral / peripheral vascular) **OR** Age ≥55 (men) / 60 (women), and dyslipidemia / HT / active smoking	3.5 per 100 pt-yrs
TECOS	H/o major CAD / ischemic cerebrovascular disease, or atherosclerotic PAD	3.6 per 100 pt-yrs
EMPA-REG OUTCOME	Single-vessel CAD / Multi-vessel CAD / PAD / $H_{/o}$ MI / $H_{/o}$ Stroke / $H_{/o}$ UA with CAD	4.4 per 100 pt-yrs
CANVAS Program	Age ≥30, with Symptomatic ASCVD Age ≥50, with ≥2 CV risk-factors	3.2 per 100 pt-yrs

Fig 2 — 3P-MACE Event Rates in CVOTs (Placebo Groups)

In the CANVAS program, in the subgroup of patients with multiple CV risk factors,a meaningful effect was not demonstrated for 3P-MACE (hazard ratio was 0.98), although the p-value for interaction was non-significant.This means that although the overall results of 3P-MACE were consistent across the subgroups, a clear benefit was not demonstrated in patients with multiple CV risk-factors. A CV safety meta-analysis of empagliflozin, including pooled events from 8 randomized controlled trials, demonstrated consistent CV benefitswith empagliflozin in patients of T2DM with low-medium or high CV risk. On exclusion of EMPA-REG OUTCOME study from this analysis, significant CV benefits still remained for 4P-MACE and hospitalizations for heart-failure or CV death. However, this meta-analysis included trials of 24-52 weeks duration, and fewer CV events. Hence, this evidence of possible CV benefit with empagliflozin, in patients with lower CV-risk profiles, is also exploratory in nature[26].

Real-world studies like CVD-REAL study furnish additional evidence of possible CV benefitsof the SGLT2-i agents, in patients with varied extent of CV-risks.27In thisretrospective real-world analysis including diverse database records, the use of SGLT-2i agents was associated with significant 51% lower risk of mortality, and 39% lower risk of HHF. The analysis does suggest an overall benefit of SGLT2-i agents compared to the other glucose-lowering therapies. However, real-world evidence does not give a conclusive proof, because of the inherent limita-

tions in such observational study designs. In CVD REAL study, the two comparator groups were matched for only[28-34] possible confounding variables, through 1:1 propensity-score matching.Acleardiscordancewas observed in the findings of the US-cohort of CVD-REAL study. This US-cohort included patients who mainly received canagliflozin. A significant reduction in all-cause death was observed in this US cohort;however, in the CANVAS program, canagliflozin failed to demonstrate a benefit for all-cause death.This discordance is possibly explained by immortal time bias, which maybe prevalent in real-world studies, as explained earlier[29].

Conclusion :

Hence, contemporary evidence does not confirm the possibility of primary CVD prevention with SGLT2-i agents, as far as the 3P-MACE outcomes are concerned. The diverse cardio-metaboliceffects of SGLT2-inhibitiors, like improvement in blood pressure, reduction in interstitial fluid volume, reduction in arterial stiffness, delay in onset and progression of chronic kidney disease, or lusitropic effect, suggest possible benefits of preventing CVD, if used optimally in patients of T2DM with apposite risk.

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Activities Report

IMA Kottakkal Branch organised CME Programme

IMA Vatakara Br. Observed Breast Feeding Week, Face to Face & World Heart Day Programme

IMA Sulthan Bathery Branch Organised CME, Quiz, Medical Camps, Distribution water purifiers.
Branch also Distributed Note books, Umbrella, Pen, Pincil, School bags, etc, at Pulijal-Vellamunda Flood Relif Camp

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Authorship: All persons designated as authors should **qualify for authorship.** Authorship credit should be based only on **significant contributions** to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. **Conditions (a), (b) and (c) must all be met.** Authors may include explanation of each author's contribution separately.

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Title page— The title page should include the title of the article which should be concise but informative, name(s) of author(s) with his/her (their) academic qualification(s) and designation(s), and complete postal address including pin code of the institution(s) to which the work should be attributed.

Abstract— The 2nd page should carry an abstract of no more than 250 words and should contain the purposes of the study or investigations, basic procedure, main findings and their implications along with Key words.

Text— The text of Originals and Papers should conform to the conventional division of abstract, introduction, material and method, observations, discussion and references. Other types of articles such as Practitioners' Series, Case Notes, Current Topics, GP Forum, etc, are likely to need other formats.

Statistical evaluation—Description of the statistical methods used should either be given in detail in the "material and method" section of the article or supportive reference may be cited.

Abbreviations— Standard abbreviations should be used and **be spelt out when first used in the text.** Abbreviations should not be used in the title or abstract.

Units of measurement— Metric units should be used in scientific contributions. If the conventional units or SI units were actually followed in measurements that should be given in parentheses.

Drugs— The **generic names of the drugs (and not proprietary names)** including dose(s), route(s) and period of administration should be mentioned.

Length of manuscripts— For Originals and Papers, Practitioners'Series, Preliminary Report, GP Forum and Current Topics: Maximum 2000-2200 words, 2-3 figures, and/or 2-4 tables, for Case Notes: Maximum 800 words, 2 figures, 1 table, for Letter to the Editor: 300-500 words.

[1]International Committee of Medical Journal Editors—Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *JAMA* 1997; **277:** 927-34.

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Reference from book :

[2]Handin RI— Bleeding and thrombosis. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, *et al* editors—Harrison's Principles of Internal Medicine. Vol 1. 12th ed. New York: Mc Graw Hill Inc, 1991: 348-53.

Reference from electronic media :

[3]National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): **7-18.**

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—Hony Editor
Journal of the Indian Medical Association (JIMA),
53, Sir Nilratan Sirkar Sarani (Creek Row), Kolkata - 700014
Phone : (033) 2236-0573, 2237-8092, Fax : (033) 2236-6437
E-mail : jima1930@rediffmail.com

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION:
Sir Nilratan Sircar IMA House, 53 Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phones: (033) 2236-0573, 2237-8092, Fax: (033) 2236-6437, E-mail : jima1930@rediffmail.com,
Website: www.ejima.in ; www.ima-india.org, www.ima-india.org/ejima
Head office: Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones: +91-11-2337 0009, 2337 8680, Fax: +91-11-2337 9470, 2337 0375,
Telegram: INMEDICI, New Delhi - 110 002, Email: hsg@ima-india.org; Website: www.ima-india.org

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