₹10

JIMA

Volume 63 (RNI) ◆ Number 11 ◆ November 2019 ◆ Kolkata

JOURNAL of the INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in Index Medicus INDEX COPERNICUS INTERNATIONAL

Volume 117 (JIMA) ♦ Number 11 ♦ November 2019 ♦ Kolkata

Special Supplement on Diabetes

Largest Circulated Medical Journal in India

ISSN 0019-5847

90TH YEAR OF PUBLICATION

Visit us at http://www.ejima.in

Newly Launched https://onlinejima.com

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION

OFFICE BEARERS OF IMA (HQS)

National President
Dr. Santanu Sen (Bengal)
Honorary Secretary General
Dr. R. V. Asokan (Kerala)
Immediate Past National President
Dr. Ravi S.Wankhedkar (Maharashtra)
National President-Elect (2019-2020)
Dr. Rajan Sharma (Haryana)
National Vice-Presidents
Dr. J. A. Jayalal (Tamil Nadu)
Dr. Pragnesh C. Joshi (Gujarat)
Dr. P. Gangadhara Rao (Andhra Pradesh)
Dr. Anil S. Pachnekar (Maharashtra)
Honorary Finance Secretary
Dr. Ramesh Kumar Datta (Delhi)
Honorary Joint Secretaries
Dr. Vijay Kumar Malhotra (Delhi)
Dr. V. K. Arora (Delhi)
Dr. Amrit Pal Singh (Delhi)
Dr. Pijush Kanti Roy (Bengal)
Dr. Sibabrata Banerjee (Bengal)
Honorary Assistant Secretaries
Dr. Usha Sridhar (Delhi)
Dr. S. K. Poddar (Delhi)
HonoraryJoint Finance Secretaries
Dr. Dinesh Sahai (Delhi)
Dr. Iskandar Hossain (Bengal)
IMA CGP (Chennai)
Dean of Studies
Dr. Sudhir Dhakre (Uttar Pradesh)
Honorary Secretary
Dr. L. Yesodha (Tamil Nadu)
IMA AMS (Hyderabad)
Chairman
Dr. Natwar Sharda (Madhya Pradesh)
Honorary Secretary
Dr. Mohan Gupta (Telangana)
IMA AKN Sinha Institute (Patna)
Director
Dr. Paramjit Singh Bakhshi (Punjab)
Honorary Executive Secretary
Dr. Ajay Kumar (Bihar)
JIMA (Calcutta)
Honorary Editor
Dr. Golokbihari Maji (Bengal)
Honorary Secretary
Dr. Sanjoy Banerjee (Bengal)
Indian Medical Journal (Delhi)
Chairman
Dr. Ravi S. Wankhedkar (Maharashtra)
Editor-in-Chief
Dr. Vedprakash Mishra (Maharashtra)
Your Health (Calcutta)
Honorary Editor
Dr. Nandita Chakrabarti (Bengal)
Honorary Secretary
Dr. Kakali Sen (Bengal)
IMA N.S.S.S. (Ahmedabad)
Chairman
Dr. Kirti M. Patel (Gujarat)
Honorary Secretary
Dr. Yogendra S. Modi (Gujarat)
IMA N.P.P.Scheme
(Thiruvananthapuram)
Chairman
Dr. Krishna M. Parate (Maharashtra)
Honorary Secretary
Dr. Jayakrishnan A. V. (Kerala)
Apka Swasthya (Varanasi)
Honorary Editor
Dr. Manoj Kumar Srivastava
(Uttar Pradesh)
Honorary Secretary
Dr. Ashok Rai (Uttar Pradesh)
IMA Hospital Board of India
Chairman
Dr. Vinod Kumar Monga (Delhi)
Honorary Secretary
Dr. Jayesh M. Lele (Maharashtra)
IMA Women Doctors Wing
Chairman
Dr. Mona Desai (Gujarat)
Honorary Secretary
Dr. Neeta S. Biyani(Maharashtra)
IMA Mission Pink Health
Chairman
Dr. Vijaya Mali (Maharashtra)
Honorary Secretary
Dr. Vibha Tandon (Delhi)
IMA Junior Doctors' Network
Chairman
Dr. Adit Desai (Gujarat)
Honorary Secretary
Dr. K. M. Abul Hasan (Tamil Nadu)
IMA Medical Students' Network
Chairman
Dr. Sreejith N. Kumar(Kerala)
Honorary Secretary
Dr. Ajoy Kumar Saha (Maharashtra)
IMA National Health Scheme
Chairman
Dr. Ashok S. Adhao (Maharashtra)
Honorary Secretary
Dr. Alex Franklin (Kerala)
IMA National Pension Scheme
Chairman
Dr. Prashant Nikhade (Maharashtra)
Honorary Secretary
Dr. P. Gopeenathan (Kerala)
IMA National Family Welfare Scheme
Chairman
Dr. K. Vijayakumar (Tamil Nadu)
Honorary Secretary
Dr. V. Sasidharan Pillai (Kerala)

Two Feathers in the Cap of Team JIMA in 2019

JIMA goes SMART

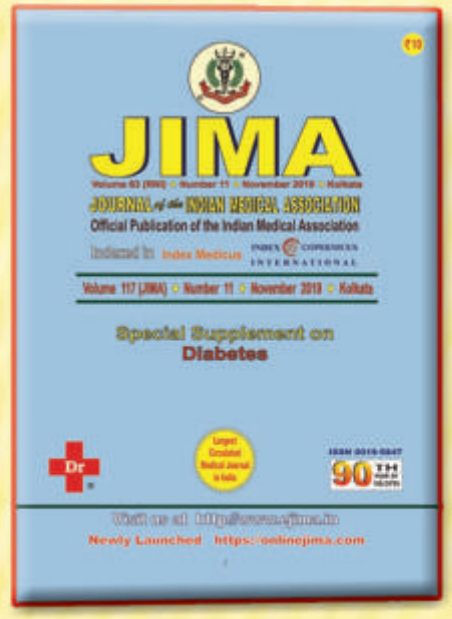
For JIO Users

- Download 'JIOCHAT' App
- Search on JioChannel for 'Journal of IMA'
- Touch the link you received
- Download the 'jionews' App
- Search for 'JIMA' in jionews

For Non JIO Users

- Download the "jionews" App
- Search for 'JIMA' in jionews

INDEX COPERNICUS INTERNATIONAL



Please log on:

https://journals.indexcopernicus.com/search/details?id=37323&lang=pl

JOURNAL of the INDIAN MEDICAL ASSOCIATION

Volume 117 • Number 11 • Kolkata • November 2019 ISSN 0019-5847

CONTENTS

Editorial

Medical Tourism

Dr Golokbihari Maji
MS (Ortho)
Hony Editor, Journal of IMA (JIMA)

Medical tourism involves patients travelling from their home country to foreign country, where they must make arrangements for their treatment and stay. When seeking care in a foreign country, patients use various agents including insurance companies and healthcare providers. It is a concept wherein people travel to another city or country to get medical treatment, to find a cheaper place for the medical procedures of same quality. In some countries certain medical procedures are not legal, such as infertility procedures. Mostly, people around the world travel to Medical centres in well developed countries, to receive good quality of treatments. But in recent years, we can see a rise in the people from well developed countries, travelling to third – world countries for medical treatments. This is mostly because of the treatment available in such countries are very low in cost.

10 best countries for medical tourism and overseas healthcare are:

Brazil	–	For fantastic plastic surgery,
Mexico	–	Most affordable dental services,
Panama	–	General health care,
Czech Republic	–	Cosmetic surgeries and teeth whitening,
Costa Rica	–	General health care and dental care,
Turkey	–	Eye health care,
India	–	Top destination for serious surgical procedures,
Thailand	–	Cosmetic surgeries,
Singapore	–	Replacement surgeries of hip and knee,
Malaysia	–	Vitro fertilization.

Yet there are certain risks of Medical tourism, some of which are mentioned below:

- Communication may be a problem,
- Medication may be counterfeit or of poor quality in some countries,
- Antibiotic resistance is a global problem, and resistant bacteria may be more common in other countries than in United States,
- Flying after surgery can increase the risk of blood clots.

From the latest report, Finland is found to have the best health care system in the World, it is also the 14th best country over all.

The first recorded instance of people travelling for medical treatment dates back thousands of years to when Greek pilgrims travelled from the eastern Mediterranean to a small area in the saronic Gulf called Epidauria. This territory was the sanctuary of the healing god Asklepios spa towns and sanitaria were early forms of medical tourism. In 18th Century Europe, patients visited spas because these were places with supposedly health – giving mineral waters, treating diseases from gout to liver disorders and bronchitis.

Factors that have led to the increasing popularity of medical travel include the high cost of health care, long waiting times for certain procedures, the ease and affordability of international level and improvement of both technology and standard of care in many countries. The avoidance of waiting time is the leading factor for medical tourism from the UK, whereas in the US, the main reason is cheaper price abroad. Furthermore, death rates even in developed countries differ extremely, i.e. UK verses seven other leading countries, including US. Many surgical procedures performed in medical tourism destinations cost a fraction of the price they do in other countries. In the United States, a liver transplant that may cost $ 300,000 USD, would generally cost about $ 91,000 USD in Taiwan. A large draw to medical travel is convenience and speed. Countries that operate public health care systems often have long wait times for certain operations for example an estimated 78236 Canadian patients spent an average waiting time of 9.4 weeks on medical waiting list in a year. Canada has also set waiting time bench marks for non-urgent medical procedures, including 26 weeks waiting period for a hip replacement and 16 weeks wait for cataract operation.

However, perception of medical tourism are not always positive. In places like the US, which has high standard of quality, medical tourism is viewed as risky. In some parts of the world, wider political issues can influence where medical tourist will choose to seek out health care.

Circumvention tourism is also an area of medical tourism that has grown. Circumvention tourism is travel in order to access medical services that are legal in destination country but illegal in the home country. This can include travel for fertility treatment that are not yet approved in the home country, abortion and doctor- assisted suicide. Abortion tourism most commonly found in Europe, where travel between countries is relatively simple. Ireland and Poland, two European countries with highly restrictive abortion laws, have the highest rates of circumvention tourism. In Poland especially, it is estimated that each year nearly 7000 women travel to UK, where abortion services are free through the National Health Services.

Medical tourism in India :

Medical tourism is a growing sector in India. In October 2015, India's medical tourism sector was estimated to be worth US $ 3 billion. It is projected to grow at a CAGR of 200% by 2020, hitting $ 9 billion by 2020. In 2017, 495,056 patients visited to seek medical care. The top 10 sources countries for patients were Bangladesh, Afganistan, Iraq, Maldives, Oman, Yemen, Uzbekistan, Kenya, Nigeria and Tanzania.

To encourage applications and care the travel process for medical tourists, the government has expanded its e-tourism VISA regime on February 2019, to include medical visas. The maximum duration to stay under this visa is 6 months.

The promotion of Medical Tourism in India has helped private players capatalize on this market opportunity. Private institutions and organizations, such as Max Healthcare where Health Travelers worldwide have consulted and treated upto 50,000 foreign patients in hospitals across the country.

Attractions :

Advantage of medical treatment in India include reduced cost, the availability of latest medical technologies and a growing compliance on international quality standard, doctors trained in western countries including Unites States and United Kingdom, as well as English speaking personnel, due to which foreigners are less likely to face language barrier in India.

Advantages :

Cost – Most estimates found that treatment cost in India start at around one –tenth of the price of comparable treatment in United States and United Kingdom. The most popular treatments sought in India by medical tourists are alternative medicine, bone –marrow transplant, cardiac bypass, eye surgery and hip replacement.

Quality Care :

India has 39 JCI accredited hospitals. However, for a patient travelling to India, it is important to find the optimal doctor-hospital combination. After the patient has been treated, the patient has the option of either recuperating in the hospital or at a paid accommodation nearby. Many hospitals also give the option of continuing the treatment through telemedicine.

The city of Chennai has been termed as "India's health capital." Multi and super speciality hospitals across the city bring in an estimated 150 international patients every day. Chennai attracts about 45 percent of health tourists from abroad arriving in the country and 30 to 40 percent domestic health tourists. Factors behind the tourist inflow in the city include low costs, little to no waiting period, and facilities offered at the specialty hospitals in the city. The city has an estimated 12,500 hospital beds, of which only half in used by city population with rest being shared by patients from other states of the country and foreigners. Dental clinics have attracted dental care tourism in Chennai.

Ease of Travel :

The government has removed visa restrictions on tourist visa that required a two months gap between consecutive visits for people from Gulf countries, which is likely to boost medical tourism. A visa–on–arrival scheme for tourists from selected countries has been instituted which allows foreign nationals to stay in India for 30 days for medical reasons. From 2016 citizens from Bangladesh, Afganistan, Maldives. Republic of Korea and Nigeria are availing the most medical visas.

Language :

Despite India's diversity of languages, English is an official language and is widely spoken by most people and almost universally by medical professionals. A number of hospitals have hired language translators to make patients from Balkan and Afraican countries feel more comfortable while at the same time helping the facilitation of their treatment.

Top medical Tourism destinations in India:-

- Chennai
- Mumbai
- New Delhi
- Calcutta
- Goa
- Banglaroe
- Ahmedabad
- Coimbatore
- Vellore
- Alleppy
- Hyderabad

The names of popular healthcare providers in India are given below : –

Apollo Hospitals
Max Hospitals
Fortis Hospitals
Kokilaben Dhirubhai Ambani Hospitals
Wockhardt Hospital
Narayana Hrudayalaya Hospitals
Metro Group of Hospitals
Manipal Hospitals
Medanta Hospitals

India is becoming the 2nd Medical tourism destination after Thailand. As medical treatment costs in the developed world is ballooning with United States leading the way, more and more westerns are finding the prospect of international travel for medical care increasingly appalling. An estimated 15,0000 of these travel to India for low priced health care procedures every year. Cosmetic surgery, bariatric surgery, knee cap transplantation, liver transplants and cancer treatment are some of the most sought out medical tourism procedures chosen by foreigners.

Guest Editorial

Dr Sujoy Ghosh
MD, DM, MRCP, FRCP,
Associate Professor, Department of Endocrinology and Metabolism, IPGME&R, Kolkata 700020
Hony Guest Editor, JIMA

Dr Pradip Mukhopadhyay
MD, DM (Endo),
Associate Professor, Department of Endocrinology and Metabolism, IPGME&R, Kolkata 700020
Hony Guest Editor, JIMA

Diabetes and Artificial Intelligence

Several innovative advances in the field of science and technology are going to be integral to the lives of subjects living with diabetes. These innovations improve the QoL (quality of life) by decreasing mortality and morbidity significantly. Intelligent closed loop insulin pumps (artificial pancreas), non-invasive glucose sensors are concepts, already established in the field of diabetes management. Artificial intelligence (AI) is also a rapidly emerging tool for managing diabetes more efficiently. AI enables computers to sort problems by synchronous use of these innovations which otherwise require human intelligence. In fact, AI is a branch of computer science that aims to create systems or methods that analyze information and allow the handling of complexity in a wide range of applications without direct human intervention[1].

Diabetes mellitus is one of the most prevalent chronic diseases associated with multi-organ morbidity and significant mortality. The hallmark of diabetes is dysregulation of glucose homeostasis. AI methods in combination with the latest technologies, including medical devices, mobile computing, and sensor technologies, have the potential to enable the creation and delivery of better management services to deal with chronic diseases like diabetes[1].

How does AI Operate Conceptually ?

The application of AI algorithm is highly complex and involves technical and specialized knowledge. In brief, the first and most important part of this method is acquiring information which is popularly known as 'Learning from Knowledge'[1]. This allows computers to learn automatically without human intervention or assistance. To enable this learning, several methods or techniques are used eg, artificial neural networks, deep learning, decision trees, regression algorithms, reinforcement learning etc. The next step is 'exploration and creation of algorithms' after retrieving potential information from these databases and this is popularly known as knowledge discovery databases (KDD)[1]. In the third stage precise and effective ways are created based on reasoning from KDD and involves logical techniques such as deduction to generate conclusions[1].

Applications of AI in Diabetes: The primary areas where applications of AI are being currently evaluated in diabetes management are several[1,2]. These are in : (i) deciding blood glucose control strategies, (ii) predicting blood glucose, (iii) detecting adverse glycemic events, (iv) calculating insulin bolus, (v) determining risk and patient personalization, (vi) detecting faults and (vii) lifestyle and daily-life support in diabetes management and so on.

Continuous glucose monitoring devices in association with artificial pancreas (a closed loop insulin pump including a glucose sensor and algorithm based insulin infusion device[3]) will have the key role in the near future to improve overall diabetes management and to reduce the frequency of severe

hypoglycaemia especially in subjects with Type1 Diabetes[3]. The algorithms are based on traditional control engineering relying on either real patient's data or virtual / computer generated patient data. However AI technique in this situation uses alternative methodology to create algorithm[1]. Though there are several methodologies, the most common that is being investigated is FL (Fuzzy Logic technique)[1]. Though this fuzzy logic system has not yet been proved superior to classic algorithm, it has the ability to deal with non-linearity or uncertainty. In the feasibility trials, fuzzy method was able to improve nocturnal blood sugar control without increasing the risk of hypoglycaemia[1]. Other AI methods which are being investigated for this purpose use RL (Reinforcement Learning) or ANN (Artificial Neural Network)[1].

Excursion of blood sugar or glycemic variability is a sign of poor diabetic control. To detect this variability in real time fashion, one has to depend on CGMS with its limitations. AI techniques in the long run would be able to predict blood sugar values which could effectively prevent long term complications. ANN (Artificial Neural Network) approach in this regard, is the most widely applied methodology, but other machine learning methodologies are also being investigated[1]. Similarly, AI methods can predict episodes of extreme hyperglycaemic and hypoglycaemic fluctuations allowing the subjects or physician to act in advance to prevent any hazardous effects out of these extreme excursions[1].

Predicting and calculating bolus dose of insulin while using an insulin pump is another area where AI can have major impact in maintaining euglycemia. Presently, the mainstay to help remove the stress and guess work for rapid acting insulin is using a bolus advisor. Bolus advisors, also known as bolus calculators, are incorporated into pump technology and make the process much simpler. Bolus advisors do this by taking a few things into account: blood glucose level, target blood glucose level and carbohydrate consumption. It also takes into account any insulin still working from a previous bolus (injection of rapid acting insulin). However these bolus advisors are not free from error which may include selection of physiologically inappropriate bolus advisor settings, the use of short duration of insulin action times etc. AI has been used to provide sets of tools to improve the accuracy of carbohydrate count and to calculate the optimal insulin bolus for an ingested meal. Case-Based Reasoning (CBR) methodology has been used in this context and extensively studied at the Imperial College London[1,3]. Clinical trial has also been performed to validate their approach to manage various clinical scenarios. This approach was also demonstrated to improve glycaemic control in diabetes management when it was combined with a closed loop system. Similarly an algorithm termed as GoCARB which provides dietary advice to diabetic patients based on automatic carbohydrate counting, is being investigated by researchers at Switzerland[1]. This system uses computer vision techniques, such as feature extraction and SVM (support vector machine, another AI technology) and initial small 'proof of concept' studies show it to be an excellent assistive tool[1].

Not all subjects with diabetes are at similar risk for all the chronic diabetic complications. Presently risk factor based clinical approach or risk engine based stratification identifies the subset of patients at particular risk for a particular complication. An important step toward is to have better risk detection and intervention tailored to each and every individual separately. AI methodologies like ANN, hierarchical clustering, genetic algorithm like K-means are being evaluated more and more to stratify according to the diabetic complications eg, neuropathy, nephropathy and especially retinopathy[1,3].

Type 1 patients use CGM devices to calculate insulin infusion rates. Consequently, failure of these devices can lead to episodes of hyperglycaemia or hypoglycaemia. AI approach using SVM is shown to be able to detect correct and incorrect measurements in real-time CGM. Another AI technology KNN (k-nearest neighbour algorithm) is also being tried to diagnose faults in CGM technology[1].

Apart from these, using deep learning algorithms of AI, automated diagnosis of diabetic retinopathy (DR) and cardiovascular risk factor monitoring are now possible, which are based on large retinal fundus imaging datasets. Other AI algorithms is also likely be integrated into smart telemedicine devices and be increasingly used to provide personalized preventative programmes, as well as personalized diabetes management adapted to patients lifestyles, treatments, genetic backgrounds and environments[1,4].

So in conclusion, Artificial Intelligence (AI) in near future is going to have a tremendous impact in management of one of the most prevalent non communicable disease, diabetes mellitus.

References

1 Contreras I, Vehi J — Artificial Intelligence for Diabetes Management and Decision Support: Literature Review. *J Med Internet Res* 2018; **20(5):** e10775. doi: 10.2196/10775.

2 Dankwa-Mullan I, Rivo M, Sepulveda M, Park Y, Snowdon J, Rhee K — Transforming Diabetes Care Through Artificial Intelligence: The Future Is Here. *Popul Health Manag* 2019; **22(3):** 229-42. doi: 10.1089/pop.2018.0129.

3 Andrès E, Jeandidier N , Meyer L , Bahougne T, Zulfiqar AA, Talha S, *et al* — Currents technologies at the service of the diabetic patients: State of the art. Open access text. DOI: 10.15761/DU.1000122.

4 Fagherazzi G, Ravaud P — Digital diabetes: Perspectives for diabetes prevention, management and research. *Diabetes Metab* 2019; **45(4):** 322-9. doi: 10.1016/j.diabet.2018.08.012.

Review Article

Combination treatment with SGLT2-i and DPP4-i : Glycemic-control and beyond

Jitendra Chouhan[1], Maneesha Khalse[2]

Type 2 diabetes is chronic and progressive metabolic disorder involving multiple metabolic defects. The use of combination therapy with anti-diabetes drugs with different mechanisms of action has the potential of producing complementary metabolic action including a robust reduction in HbA1c along with cardiovascular and renal benefits. The availability of a dual sodium glucose co-transporter 2/ dipeptidyl peptidase-4 inhibitor combination represents a new therapeutic alternative for patients with type 2 diabetes. Present review considers the range of evidence for combining SGLT2-I and DPP4-I with a focus on their respective role on cardiovascular and related benefits of each agent in patients.

[*J Indian Med Assoc* 2019; **117(11)**: 14-8]

Key words **: SGLT2-i and DPP-4i combination, cardioprotection, renoprotection.**

T2 D Mellitus (T2 DM) is one of the most widely prevalent conditions causing pandemic across the globe. As evidenced by major landmark trials, although intensive glycemic control achieved by conventional agents demonstrated reduction in risk of microvascular manifestation, its relationship with macrovascular outcomes or all-cause mortality appeared to be multifaceted. Furthermore, metabolic risk factors like hypertension and obesity, and macrovascular manifestations are shown to be positively linked together for their development and progression. There is a clinical unmet need of an effective antidiabetic treatment that can ameliorate residual risk of cardiovascular disease, still having lower propensity for hypo-glycemic events and weight gain. Two classes of glucose-lowering agents that meet the criteria are sodium glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors. In 2017, Drug Controller General of India (DCGI) approved empagliflozin and linagliptin combination therapy as an adjunct to diet and exercise to improve glycemic control when treatment with both empagliflozin and linagliptin is appropriate.

Present review considers the range of evidence for combining (DPP4-i) and (SGLT2-i) with a focus on their respective role on cardiovascular and related benefits in patients.

Complementary Effects of SGLT2-i and DPP4-i Combination :

SGLT2-i is a class of novel oral glucose lowering agents that mediates glucose lowering action by increasing urinary glucose excretion via inhibition of the sodium-glucose cotransporter-2 in the proximal tubule of the kidney. The salutary effect is its ability to act independent of insulin secretion and action and render it suitable to administer at any stage of disease course. DPP4-i exerts its glucose lowering effect by the elevation of incretin hormones and subsequent augmentation of glucose dependent insulin secretion and inhibition of glucagon release. SGLT2-i associated with 17-30% rise in endogenous hepatic glucose output, perhaps mediated by compensatory increase in plasma glucagon in response to glycosuria as suggested by experimental study. Combined DPP-4i with gliflozin is speculated to prevent such increase in glucagon level resulting in optimum glucose control. Combination of these agents has potential to show the additive glycemic control due to their complementary effects (Fig 1).

Glycemic Control with Complementary Effects :

Various pivotal phase III trials suggest that combining SGLT2-i and DPP4-i in T2DM adults result in clinically

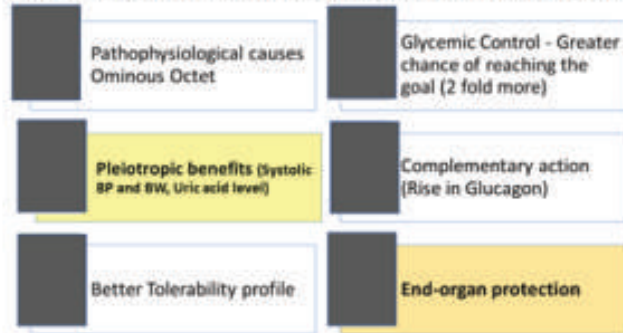


Fig 1—The need of using the combination of SGLT2-i and DPP4-i

[1]DM (Endocrinology), Assistant Professor, Department of Endocrinology, Choithram Hospital, Indore 452014
[2]MD (Pharmacology), Manager, Medical Services, Medical Affairs Division, Lupin Limited, Mumbai 400051 and Corresponding author

meaningful reductions in HbA1c (-1.2–1.5%) which was significantly more than either agent alone. In two randomized, placebo controlled trials, empagliflozin (10mg) and linagliptin (5mg) produced statistically significant reductions in HbA1c (-1.24) at week 24, in the treatment-naïve patients, and (-1.08) add on to metformin compared to linagliptin (P<0.001)[1,2]. The benefits on glycemic control were maintained at week 52 in the treatment-naïve and metformin treated groups, and a higher percentage of patients achieving HbA1c <7% were reported for combinations.

Table I — *Glycemic control with combination of SGLT2i and DPP4i versus SGLT2i or DPP-4i alone*

Combination of SGLT2-i and DPP4-i	HbA1c	FPG
vs. DPP-4i in treatment naïve	-0.69 (-1.00, -0.38)	-32.18 (-46.40, -17.96)
vs. DPP-4i on metformin background	0.70 (-0.80, -0.60)	-23.49 (-39.80, -7.17)
vs. SGLT2i in treatment naïve	-0.25 (-0.34, -0.15)	-7.13 (-13.28, -0.97)
vs. SGLT2i on metformin background	-0.38 (-0.48, -0.28)	-10.55 (-13.58, -7.52)

Adapted from Li et al.meta-analysis (2018).

Results were consistent with other combination therapy like dapagliflozin and saxagliptin in patients with uncontrolled glycemia[3]. Large metaanalysis with different combination agents analyzed glucose lowering potential with consistent results (Table 1).

End Organ Protection :

Hypertension and cardiovascular disease (CVD) are the most common comorbidities in T2D patients[4]. Overall, CVD with significant morbidity and mortality accounts for half (50.3%) of deaths in this population[5]. Approximately 40% of patients with diabetes upon screening for decreased eGFR and albuminuria have evidence of CKD[6].

Cardiovascular Benefits :

Due to the conflicting reports of increased risk of cardiovascular event with antidiabetic agents, USFDA (2008)[7]and EMA (2012)[8] issued a guidance to provide CV safety data for new antidiabetic medications. Empagliflozin was first SGLT2-i to demonstrate cardio-renal benefit in T2D patients with established cardiovascular disease (eCVD) (99% of cohort)[9]. DPP4-i demonstrated CV safety in patients, although with increased risk of heart failure reported with saxagliptin that led to the incorporation of heart failure risk warning in all USFDA-approved DPP4-i labels in August 2017[10]. Combinations of SGLT2-i and DPP4-i are not retested in similar clinical trial programs to the individual drug because the agents are bioequivalent[11].

Empagliflozin Cardiovascular Outcome Event Trial in T2D Mellitus Patients (EMPA-REG OUTCOME) reported that 3P-MACE outcome occurred in a significantly lower percentage (HR 0.86; 95.02% CI: 0.74-0.99; P = 0.04) in the Empagliflozin compared to placebo on top of standard care. Treatment with Empagliflozin resulted in a 38% (HR 0.62, 95% CI 0.49, 0.77p<0.001) reduction of death from CV causes, and 35% reduction of hospitalization for HF (HR 0.65, 95% CI 0.50, 0.85; p <0.002)[12]. There were around 11% patients on DPP4-i in background therapy. Empagliflozin is the only SGLT2i (FDA 2016) to reduce the risk of CV death in patients with T2D and established CV disease to date[13].

In CANVAS program, a total of 10,142 patients with T2 DM and either established CV disease or multiple CV risk factors (34.4%) demonstrated a significant reduction (by 14%) in the composite primary endpoint (HR 0.86, 95% CI 0.75, 0.97) in canagliflozin group compared to placebo[14]. A total of 17,160 patients with T2 DM were assessed for CV Safety in Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) study for a median period of 4.2 years[15]. Treatment with Dapagliflozin resulted in a 17% reduction of the composite outcome of CV death or hospitalization for HF, while no effect was reported for the 3P-MACE[16].

Mechanism behind the impressive CV benefits exhibited by SGLT2-i is mostly unknown, however, closely interconnected to its hemodynamic effects (Fig 2).

With the range of evidence with DPP4-i, overall cardiac safety was quite evident in patients with high risk of cardiovascular disease compared to placebo.

CV safety of DPP4-i further elucidated in CARMELINA (CARdiovascular Safety & Clinical outcoME with LINAgliptin) trial in T2D patients with renal impairment which recruited a substantial proportion of patients with T2 DM; 74% had prevalent kidney disease. Linagliptin has demonstrated the CV and renal safety (secondary

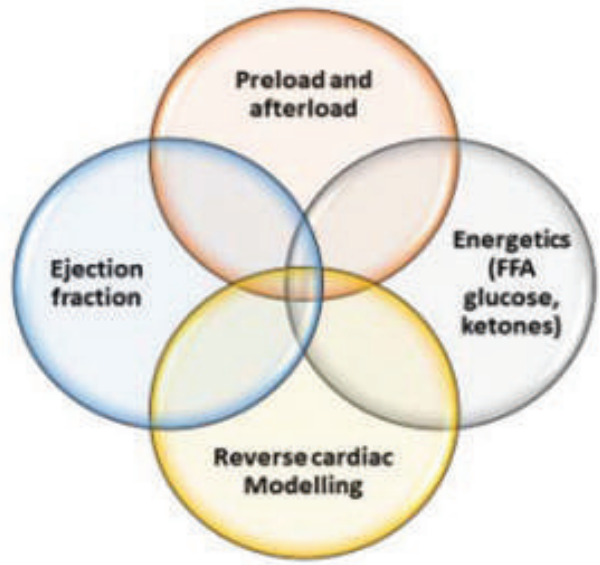


Fig 2 — Proposed mechanism for cardiovascular benefits of empagliflozin

endpoint) of linagliptin versus placebo when in addition to standard care in patients with T2 DM who were at high risk of vascular complications[17]. CAROLINA (Cardiovascular Outcome Study of LINAgliptin versus Glimepiride in Patients with Type 2 Diabete) trial similarly demonstrated CV safety compared to active comparator in 6041 patients with relatively early T2 DM[18].

Preservation of Renal Function :

Growing evidence showed that SGLT2-i has the potential to offer renoprotective effects in patients with T2 DM and CKD. In a sub-analysis from EMPA Reg study, empagliflozin decreased new-onset or worsening of nephropathy by 39% (HR 0.61, 95% CI 0.53–0.70) as compared to placebo, on the top of RAS-blocker therapy[19]. Although HbA1c reduction observed with SGLT2-i declines with progressive eGFR reduction, the CV and renal benefits seem to be maintained independent of eGFR level (< 30 mL/min/1.73 m2). SGLT2-I demonstrated preservation of eGFR, as compared to glimepiride or placebo in a four-year duration studies[20].

Restoration of tubule-glomerular feedback reducing intraglomerular pressure and decreased glomerular hyperfiltration, have been postulated for renal benefits of SGLT2-i[21]. Initially after institution of therapy, clinical presentation may report a decline in eGFR value by 4-5 mL/min/1.73 m^2 during the first weeks of treatment and then gradually improve after 6-12 months[22,23] with stabilization of renal function.

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial which is first dedicated renal outcomes trials for canagliflozin reported renal benefits including patients with eGFR value of 30ml/min/1.73m^2.

DPP4-i may have beneficial effects on renal outcomes primarily by reducing albuminuria compared to placebo in patients with T2D.

Extra Glycemic Effects :

Body weight reduction :

In contrast to conventional anti-glycemic agents, SGLT2-i demonstrated moderate weight loss in patients, mechanism mostly unknown. It is estimated that 75 gm glucose per day are lost in the urine with a diuresis of 400 mL/day. The EMPA-REG study showed that patients on empagliflozin 10 and 25 mg lost a mean of around 2 kg and almost 3 kg of body weight, respectively. Weight loss seem to occur rapidly in the first weeks of treatment, followed by gradual decline which reaches a plateau after 6 months and is maintained for a long time.

Blood pressure lowering :

It is widely known that the reduction of arterial BP is closely linked to reduction of CV morbidity and mortality in patients with DM[24]. More specifically, SGLT2-i reduce 24-h ambulatory systolic and diastolic BP by 3.76 mmHg and 1.83 mmHg, respectively[25,26]. Several mechanism has been suggested like plasma volume contraction; weight loss; improvements in vascular stiffness by reductions in body weight, reduced sympathetic nervous system activity; and lower serum uric acid concentrations[27].

Arterial Stiffness :

Diabetes is likely to be closely linked to the increased arterial stiffness without coexisting hypertension.

SGLT2-i has also shown amelioration of aortic stiffness measured noninvasively[28]. SGLT2i induce natriuresis, which might improve whole-body sodium balance and volume status[29], and are associated with improved endothelial function and reduced vascular stiffening, decreasing the demand placed on cardiac tissue that causes left ventricular hypertrophy[30].

Effect on liver fat :

SGLT2is (empagliflozin, luseogliflozin, canagliflozin) attenuate several factors associated with nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), such as weight gain, elevated alanine amino-transferase, high liver fat index, and visceral fat[31].

Post-hoc study of EMPA Reg showed the improvement in amino-transferase level at 28 week [-2.98 ±0.18 versus placebo -0.73±0.25U/L ($p<0.0001$)]. In (E-LIFT) trial[32] empagliflozin was significantly better at reducing liver fat over control in standard of care diabetes treatment.

Lipid modifying effects:

Dyslipidemia is a common comorbidity of T2 DM that increases CV morbidity and mortality[33]. The administration of Empagliflozin or Canagliflozin increased both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) according to the EMPA-Reg outcome and CANVAS program. SGLT2-i administration modestly alter lipid profiles by reductions in plasma triglycerides and increase in HDL cholesterol and LDL cholesterol[34,35], while triglyceride and small dense LDL levels tend to modestly decrease SGLT2is[36].

Uric acid lowering effect :

Elevated uric acid in T2D is a common finding in metabolic syndrome. The mechanism is not clearly understood. However, some studies suggested that it may possibly involve the renal SLC2A9 (GLUT9) transporter[37]. A recent post hoc analysis of EMPA-REG trial has shown that 24.6% of the empagliflozin effect on the observed decrease in the risk of cardiovascular death may be mediated by changes in uric acid[38].

Tolerability Profile :

Combination therapy of SGLT-2i and DPP4-i was observed to have less risk of hypoglycemia (2.4%)

compared to either drug alone. Most of the studies reported similar genitourinary infection in combination arm, compared to SGLT2-i alone which is intrinsic to the mode of action of SGLT-2i. Frequent adverse reaction observed with 10 mg empagliflozin / 5 mg linagliptin and (8.50 % with 25 mg empagliflozin / 5 mg linagliptin) was urinary tract infection (7.5 %). Interestingly, the rate of genital infections is lowered by 26% when used with the combination, which has been postulated to be attributed to DPP-4i effect on the immune system[39]. The adverse reactions like ketoacidosis (<0.1%), pancreatitis (0.2%) were rare with this combination. Certain precautions advised during the administration and follow-up are to check eGFR periodically, to check electrolytes level, background therapies like diuretic, Insulin and insulin secretagogues, reinforcement on advice of perineal hygiene, advice on the fasting, keto diet or acute illness, watch on serum creatinine level.

Current Place of SGLT2i and DPP4-i in T2D Management :

Empagliflozin and linagliptin is the first-in class available combination of SGLT2-i and DPP4-i in India. This anti-diabetic class appear to be a promising add-on in therapeutic armamentarium of T2D management due to their various complementary effects on incretin and renal glucose excretion, more proportion of patients achieving target than either drug alone, better tolerability profile with substantial cardiorenal benefits. ADA (2016) guidelines on use of triple drug combination suggests that if A1c targets are not achieved after 3 months of dual therapy, begin triple therapy by adding third hypoglycemic agent to the dual combination.

Summaries of product characteristics suggests that DPP-4/SGLT2i combinations can be instituted in case of inadequate glycemic control with metformin and/or sulphonylureas (SU) or when already being treated with the free combination of individual components. Rather than using a conventional stepwise treatment strategy, early use of triple therapy (add-on dual therapy to metformin) could be considered in patients who have failed to achieve glycemic control on metformin. SGLT-2i are not recommended in patients with advanced kidney disease (eGFR <45 mL/min/1.73 m2 for canagliflozin, dapagliflozin and empagliflozin and <60 mL/ min/1.73 m^2 for ertugliflozin).

Conclusion :

In the era of patient-centered care, the novel combination of SGLT2-i and DPP4-i by virtue of its unique features will prove as an important contribution in diabetes health care system to address the medical unmet need of ever growing epidemic of diabetes in Indian population.

References

1 Lewin A, DeFronzo RA, Patel S, Liu D, Kaste R, Woerle HJ, *et al* — Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. *Diabetes Care* 2015; **38(3):** 394-402.

2 DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, *et al* — Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care* 2015; **38 (3):** 384-93.

3 Rosenstock J, Hansen L, Zee P — Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. *Diabetes Care* 2015; **38(3):** 376-83.

4 Pantalone KM, Hobbs TM, Wells BJ, Li Y, Cook W, Hirshberg B, *et al* — Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. *BMJ Open Diabetes Res Care* 2015; **3:** e000093.

5 Einarson TR, Acs A, Ludwig C, Panton UH — Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol* 2018; **17(1):** 83.

6 Garg AX, Kiberd B a, Clark WF, Haynes RB, Clase CM — Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002; **61(6):** 2165-75.

7 FDA Guidance for Industry. Diabestes mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Washington DC: US Food and Drug Administration; 2008.

8 CHMP (Committee for Medicinal Products for Human Use) Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. CPMP/EWP/1080/00 Rev. 1. London: European Medicines Agency; 2012

9 Zinman B, Wanner C, Lachin JM — EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373:** 2117-28.

10 http://www.diabetesincontrol.com/heart-failure-warning-added-to-the-dpp-4-inhibitor-class-of-drugs/ (Last accessed on 29 September 2019)

11 Scheen AJ — Pharmacokinetic Characteristics and Clinical Efficacy of an SGLT2i Plus DPP-4 Inhibitor Combination Therapy in Type 2 Diabetes. Clin Pharmacokinet 2016.

12 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al* — EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373(22):** 2117-28.

13 American Diabetes Association. Standards of Medical Care in Diabetes-2018 Abridged for Primary Care Providers. *Clin Diabetes* 2018; **36(1):** 14-37

14 Neal B, Perkovic V, Mahaffey KW — Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377(7):** 644-57.

15 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al* — Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380(4):** 347-57.

16 Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, *et al* — Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Out- comes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017; **136(3):** 249-59.

17 Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, *et al* — Effect of Linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA* 2019; **321(1):** 69-79.

18 Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, *et al* — T Effect of linagliptin *versus* glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA* 2019.

19 Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, *et al* — Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375(4):** 323-34.

20 Salsali A, Ridderstrale M, Toorawa R — Empagliflozin compared with glimepiride as add-on to metformin for 4 years in patients with type 2 diabetes. Presented at American Diabetes Association 76th Scientific Sessions; New Orleans, Louisiana, USA, 2016.

21 de Albuquerque Rocha N, Neeland IJ, McCullough PA, Toto RD, McGuire DK — Effects of sodium glucose co-transporter 2 inhibitors on the kidney. *Diab Vasc Dis Res* 2018; **15(5):** 375-86.

22 DeFronzo RA, Norton L, Abdul-Ghani M — Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. *Nat Rev Nephrol* 2017; **13(1):** 11-26.

23 Alicic RZ, Johnson EJ, Tuttle KR — SGLT2 Inhibition for the Prevention and Treatment of Diabetic Kidney Disease: A Review. *Am J Kidney Dis* 2018; **72(2):** 267-77.

24 Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, *et al* — Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *BMJ* 2000; **321:** 412-9.

25 Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, *et al* — Effects of Sodium-Glucose Cotransporter 2 Inhibitors on 24-Hour Ambulatory Blood Pressure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2017; **6.**

26 Lipid-Lowering Treatment to Prevent Heart Attack, T Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981-97.

27 Muskiet MHA, van Bommel EJM, van Raalte DH — Antihypertensive effects of SGLT2-i in type 2 diabetes. *Lancet Diabetes Endocrinol* 2016; **4:** 188-9.

28 Chilton R, Tikkanen I, Cannon CP — Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metab* 2015; **17(12):** 1180-93.

29 Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ — Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016; **134(10):** 752-72.

30 Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI — Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation* 2017; **136(17):** 1643-58.

31 Sumida Y, Yoneda M — Current and future pharmacological therapies for NAFLD/NASH. *J Gastroenterol* 2018; **53(3):** 362-76.

32 Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, *et al* — Effect 637 of empagliflozin on liver fat in patients with type 2 diabetes and non-alcoholic 638 fatty liver disease: a randomized controlled trial (E-LIFT Trial). *Diabetes Care* 2018; **41:** 1801-8.

33 Verges B — Pathophysiology of diabetic dyslipidaemia: Where are we? *Diabetologia* 2015; **58:** 886-99.

34 Filippas-Ntekouan S, Tsimihodimos V, Filippatos T, Dimitriou T, Elisaf M — SGLT-2 inhibitors: Pharmacokinetics characteristics and effects on lipids. Expert Opin. *Drug Metab* Toxicol 2018; **14(11):** 1113-21.

35 van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH — SGLT2 inhibition in the diabetic kidney-from mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017; **12(4):** 700-10.

36 Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, Osamura A, *et al* — Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: Comparison with sitagliptin. *Cardiovasc. Diabetol* 2017; **16(1):** 8.

37 Xin Y, Guo Y, Li Y, Ma Y, Li L, Jiang H — Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: A systematic review with an indirect comparison meta-analysis. *Saudi Journal of Biological Sciences* 2019; **26(2):** 421-6.

38 Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, *et al* — How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care* 2018; **41(2):** 356-63.

39 Fadini GP, Bonora BM, Mayur S, Rigato M, Avogaro A — Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab* 2018; **20(3):** 740-44.

Review Article

Intensifying treatment for T2DM after oral therapy failure : GLP-1RA as the first injectable therapy

Gagan Priya[1], Vivek Kolapkar[2]

Since the past one decade the management of type 2 diabetes mellitus (T2DM) has evolved significantly with the addition of newer antidiabetic agents like DPP4 inhibitors, GLP-1 RAs and SGLT2 inhibitors. Among these, GLP-1 RAs offer advantages like good HbA1c reduction, weight reduction, practically no hypoglycemia, cardiovascular benefits and convenient dosing with some selected agents which can further aid in improving compliance thereby helping patients in achieving the desired glycemic goals. GLP-1 RAs are recommended by all the major guidelines across the T2DM management spectrum and are an important first injectable option after oral therapy failure. This review summarizes the data available on the usage of GLP-1 RA and their important role in the management of T2DM as a first injectable therapy.

[*J Indian Med Assoc* 2019; **117(11):** 19-22]

Key words **: GLP-1RA, dulaglutide, AWARD trial.**

Glycemic Control and Clinical Inertia in T2DM :

Type 2 diabetes mellitus (T2DM) is associated with some complex pathophysiological mechanisms contributing to hyperglycemia. To target these pathophysiological defects, different antihyperglycemic agents have been developed[1]. The response to these antihyperglycemic agents varies greatly depending on their mechanism of action[2]. Traditionally, metformin is the undisputed first line AHA in the management of T2DM. After metformin monotherapy failure several AHAs are available either oral or as injectable options for treatment intensification[2]. In the last one decade, the management of T2DM has evolved with the introduction of newer AHAs like dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose cotransporter 2 (SGLT2) inhibitors[3]. The guidelines for management of T2DM has also evolved based on the benefits seen with some of these newer AHAs in their respective cardiovascular outcome trials (CVOTs)[4].

Despite the availability of these newer and improved AHAs, T2DM patients often experience prolonged periods of suboptimal glycemic control[5,6]. According to the ICMR-INDIAB study, majority of Indian T2DM patients are sub optimally controlled with an average HbA1c hovering around 8%[7]. Typically, patients with T2DM spend approximately 6 years with an HbA1c of more than 8%. In T2DM patients who were on 3 oral AHAs and with HbA1c ≥8%, the time to additional therapy was 1.6 years for additional oral AHA and more than 6 years for insulin. Thus, there are significant delays in treatment intensification in patients with T2DM despite suboptimal glycemic control with a substantial proportion of patients experiencing poor glycemic control for several years before intensification with oral AHAs and insulin[6]. In terms of using insulin, physicians may be reluctant due to a belief about risk to patients with and without comorbidities, fear of hypoglycemia, excess weight gain, deranged quality of life, beliefs about patient competence and available resources[8,9]. These patient related factors further add to the clinical inertia compromising the ability of reaching the target HbA1c[10]. Hence, after oral therapy failure, there is a need for a noninsulin injectable AHA which can be beneficial in terms of achieving good glycemic control but mitigating the fears about safety and tolerability.

[1]DM (Endocrinology), Consultant, Department of Endocrinology, Fortis Hospital, Punjab 160047

[2]BHMS, MSc, Manager, Medical Services, Medical Affairs Division, Lupin Limited, Mumbai 400051 and Corresponding Author

Overview of Incretin-based Therapies and GLP-1RAs :

Agents in the GLP-1RA class are incretin-based therapies which are different from the DPP4 inhibitors in terms of mechanism of action mimicking the role of endogenous GLP-1, stimulating pancreatic islet cells to release insulin in response to glucose ingestion[11]. The key characteristics of incretin based therapies are illustrated in Table 1.

GLP-1RAs also inhibit glucagon release and result in good weight reduction by reducing patients' appetites due

Table 1 — *Comparison of incretin-based therapies*[8,12]

Properties/Effect	GLP-1 RAs	DPP-4 inhibitors
Route of Administration	Subcutaneous injection	Oral
Dosing	Once daily, twice daily, or once weekly depending on the agent used	Once or twice daily depending on the agent used
Glucose dependent stimulation of insulin secretion	Yes	Yes
Glucose dependent reduction of increased glucagon	Yes	Yes
HbA1c reduction	-1.1% to -1.6%	-0.6% to -1.1%
Gastric emptying	Slows gastric emptying	No effect
Food intake	Decreased	No effect
Effect on body weight	Weight loss	Weight neutral
Hypoglycemia	Nil (except when combined with insulin or sulfonylureas)	Nil (except when combined with insulin or sulfonylureas)
Adverse Effects	Nausea, vomiting, risk of pancreatitis?	Good tolerance, respiratory infections? Risk of pancreatitis?

to their ability to delay gastric emptying[12,13]. Worldwide several brands and formulations of GLP-1RAs are approved to treat T2DM, all of which have slightly different pharmacokinetic properties, clinical effects and methods of administration[14]. GLP-1RAs are broadly classified as long-acting and short-acting formulations. In India, currently there are three GLP-1 RA formulations available for clinical use (Table 2).

Short Acting GLP-1RAs :

The glycemic control achieved with short-acting GLP-1RAs is primarily driven by reductions in postprandial glucose which contributes to overall HbA1c levels[13,16]. Among the short acting GLP-1RAs,lixisenatide has been evaluated in the Get-Goal program of randomized, controlled, phase 3 clinical trialsas an intensification to basal insulin. The Get-Goal clinical trials involved different comparators including placebo, rapid acting insulin, or another GLP-1RA.The results from these studies demonstrated that once daily lixisenatide was noninferior to once or thrice daily rapid acting insulinin reducing HbA1c levels. However, lixisenatide was superior to rapid acting insulin as an add-on in achieving weight reduction[17]. According to a meta-analysis of 5 trials comparing lixisenatide vs rapid acting insulin, significantly greater proportion of patients taking lixisenatide (29%) achieved the composite end point of an HbA1c <7%, no weight gain, and no incidents of hypoglycemia as compared to patients taking rapid acting insulin (15%) (P=0.0046)[18].

Long Acting GLP-1RAs :

When it comes to lowering fasting plasma glucose levels, long-acting GLP-1RAs predominantly more effective. However, there are studies involving long-acting liraglutide and dulaglutide demonstratingreductions in postprandial glucose levels from baseline[16,19]. Dulaglutide is a once weekly GLP-1RA which is well studied in the comprehensive clinical trial programme called AWARD (Assessment of Weekly Administration of LY2189265 in Diabetes)[14]. In one such AWARD 2 randomised, 78-week, open-label study the effects of dulaglutide *versus* insulin glargine on glycaemic control was compared in adult T2DM patients uncontrolled on metformin and glimepiride. In this study, dulaglutide 1.5 mg was superior to insulin glargine and dulaglutide 0.75 mg was non-inferior to insulin glargine as measured by change in HbA1c. Throughout the trial, a higher percentage of patients on both dulaglutide doses achieved HbA1c targets of ≤6.5% and <7.0% than those on insulin glargine. At 52 weeks, the mean reduction in fasting serum glucosefrom baseline was 16 mg/dl, 27 mg/dl, and 32 mg/dl for dulaglutide 0.75 mg, dulaglutide 1.5 mg, and insulin glargine, respectively. At the 52-week primary endpoint, a greater decrease from baseline for overall daily mean PPG for dulaglutide 1.5 mg was seen. At week 52, patients receiving dulaglutide 1.5 mg achieved a mean weight loss of 1.9 kg, patients receiving dulaglutide 0.75 mg achieved a mean weight loss of 1.3 kg, and patients receiving insulin

Table 2 — *Overview of GLP-1RAs available in India*[14,15]

Properties	Dulaglutide	Liraglutide	Lixisenatide
Half life	4.7 days	13 hours	3 hours
Dosing frequency	Once weekly	Once daily	Once daily
Dose	**Monotherapy :** 0.75 mg once weekly **Add-on therapy :** 1.5 mg once weekly	1.2–1.8 mg daily	20 µg daily
Administration in relation to meals	At any time, without regard to meals	At any time, without regard to meals	Should be administered within 60 min before any meal
Single dose pen	Yes	No	No
Dose selection required	No	Yes	Yes
Dose titration	No	Yes	Yes
Needle attachment required	No. Pre-attached hidden needle	Yes. Needles ars not included	Yes. Needles are not included
Need to prime device before use	No	Yes	Yes
Automatic dose administration	Yes	No	No

glargine experienced a mean weight gain of 1.4 kg. At 78 weeks, overall safety and tolerability profiles of dulaglutide were consistent with the GLP-1 RA class, including a higher incidence of GI-related AEs with Dulaglutide than with insulin glargine. Mean rates of total and nocturnal hypoglycemia were lower compared with glargine for both dulaglutide groups[19].

In T2DM patients failing to achieve the desired HbA1c targets with triple therapy or for patients with an HbA1c of ≥10% at diagnosis, rapid-acting insulinis commonly used to augment basal insulin[2]. However, with the introduction of GLP-1RAs the treating physicians has now got an additional option for therapy intensification. According to various clinical trials GLP-1RAs have been demonstrated to be as efficacious as postprandial rapid acting insulinin improving glycemic control in patients with an inadequate response to basal insulin.The risks and benefits of RAIs and GLP-1RAs, along with treatment goals and patient preference, should be considered whenever therapy intensification is required.2In the AWARD-4 study which was a randomised, 52-week, open-label comparison of the effects of dulaglutide *versus* insulin glargine, each in combination with insulin lispro, the combination of dulaglutide and prandial insulin lispro was associated with a significantly greater improvement in glycaemic control than combined insulin glargine and prandial insulin lispro with lower risk of total and nocturnal hypoglycemia[20].

Adverse Events Associated with GLP-1RA :

None of the currently available AHAs are immune to adverse effects. Similarly, the GLP-1RAs are also associated with adverse events especially of gastrointestinal origin consisting of nausea, vomiting, and diarrhea. T2DM patients taking GLP-1RA may experience nausea, which typically resolves within the first week and rarely leads to treatment discontinuation[21]. Some patients develop upper respiratory infection or injection-site reactions[22]. It is important to inform and educate the patients about the adverse events and proper counseling should be provided as to how they can overcome and continue with the therapy. Some of the dietary measures to relieve nausea include eating small amounts of food every few hours rather than 2-3 large meals per day, avoiding greasy, fried and spicy foods[23,24].

The drug discontinuation rates due to adverse events in some of the long-term studies of GLP-1RAs have ranged from 4% to 21%[6]. Some cases of pancreatitis have been reported with GLP-1RA use, but the causality association has not yet been established[22]. When choosing a GLP-1RA the method of administration (once daily vs once weekly) delivery device, ease of use and overall safety profile must be weighed considering the patient perspective.

Role of GLP-1RA as the First Injectable Therapy :

Despite being highly effective, 43% to 50% of patients receiving basal insulin are unable to achieve the desired glycemic targets. In patients who do achieve the optimum glycemic control with basal insulin, the progression of disease compromises its effectiveness, and therefore additional AHA needs to be added[25]. The American Diabetes Association (ADA) guidelines recommend basal insulin in the presence of severe hyperglycemia, especially if symptoms are present or any catabolic features like weight loss or ketosis are present. However, considering the overall glycemic, extraglycemic and cardiovascular benefits, the ADA 2019 guidelines now recommend GLP-1RA as the first-line injectable treatment ahead of insulin for most T2DM patients who need greater efficacy of an injectable medication[2].

The guidelines also emphasize the use of GLP-1RAs with demonstrated cardiovascular disease benefit like liraglutide, dulaglutideafter metformin monotherapy failure as part of the antihyperglycemic regimen in T2DM patients with established atherosclerotic cardiovasculardisease. The GLP-1RAs are also one of the recommended options after metformin in T2DM patients without ASCVD but at risk of hypoglycemia and in those intending to achieve weight reduction[2]. Liraglutide is FDA approved to reduce the risk of MACE in adults with type 2 diabetes and established CVD; liraglutide and dulaglutide showed superiority for MACE outcomes in large CVOTs; semaglutide showed superiority for MACE outcomes in a safety CVOT however, there was also an increased risk of diabetic retinopathy[26-28]. The results from these CVOTs were primarily in patients with known ASCVD although there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD[28].

Most of the available AHAs including insulin are predominantly cleared by the kidneys and hence either require dose modification or are contraindicated in T2DM patients with chronic kidney disease (CKD)[29]. GLP-1RAs like dulaglutide are not cleared by kidney and hence their exposure is not increased in mild-to-severe renal impairment[14]. In the recently published AWARD-7 study comparing dulaglutide vs insulin glargine in patients with T2DM and moderate-to-severe CKD, both dulaglutide and insulin glargine were equally effective in glycemic reduction. However, the decline in eGFR change was significantly smaller for both dulaglutide doses compared with insulin glargine[30]. Based on this study, dulaglutide has now been recommended for use without dose adjustment in T2DM patients having eGFR upto 15 ml/min/1.73[2]. Liraglutide and semaglutide are the other GLP-1RAs having similar recommendation for use[14].

Thus, given the extensive clinical experience, demonstrated glycemic efficacy with benefits of weight reduction, no hypoglycemia, cardiovascular and renal benefits, GLP-1 RAs can be the preferred noninsulin injectable option especially in T2DM patients with established ASCVD and in T2DM patients who fail to achieve the desired glycemic control with multiple oral AHAs.

References

1 DeFronzo RA — From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; **58(4):** 773-95.

2 American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019; **42(Suppl 1):** S90-S102.

3 Davidson JA, Parente EB, Gross JL —Incretin mimetics and dipeptidyl peptidase-4 inhibitors: innovative treatment therapies for type 2 diabetes. *Arq Bras Endocrinol Metabol* 2008; **52(6):** 1039-49.

4 American Diabetes Association. Standards of Medical Care in Diabetes—2019 Abridged for Primary Care Providers. *Clinical Diabetes* 2019; **37(1):** 11-34.

5 de Pablos-Velasco P, Parhofer KG, Bradley C, Eschwège E, Gönder-Frederick L, Maheux P, *et al* — Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. *Clin Endocrinol (Oxf)* 2014; **80(1):** 47-56.

6 Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ — Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013; **36(11):** 3411-7.

7 Unnikrishnan R, Anjana RM, Deepa M, Pradeepa R, Joshi SR, Bhansali A, *et al* — *Diabetes Technol Ther* 2014; **16(9):** 596-603.

8 Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, *et al* — International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005; **28:** 2673-9.

9 Wallace TM, Matthews DR — Poor glycaemic control in type 2 diabetes: a conspiracy of disease, suboptimal therapy and attitude. *QJM* 2000; **93(6):** 369-74.

10 Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D — Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* 2017; **40(4):** 614-24.

11 Tibaldi JM — Incorporating incretin-based therapies into clinical practice for patients with type 2 diabetes. *Adv Ther* 2014; **31(3):** 289-317.

12 Scheen AJ — GLP-1 receptor agonists or DPP-4 inhibitors: how to guide the clinician? *Ann Endocrinol (Paris)* 2013; **74(5-6):** 515-22.

13 Giorgino F, Bonadonna RC, Gentile S, Vettor R, Pozzilli P — Treatment intensification in patients with inadequate glycemic control on basal insulin: rationale and clinical evidence for the use of short-acting and other glucagon-like peptide-1 receptor agonists. *Diabetes Metab Res Rev* 2016; **32(6):** 497-511.

14 Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J — A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes. *Diabetes Ther* 2019; **10(1):** 5-19.

15 Sfairopoulos D, Liatis S, Tigas S, Liberopoulos E — Clinical pharmacology of glucagon-like peptide-1 receptor agonists. *Hormones (Athens)* 2018; **17(3):** 333-350.

16 Raccah D — Basal insulin treatment intensification in patients with type 2 diabetes mellitus: a comprehensive systematic review of current options. *Diabetes Metab* 2017; **43(2):** 110-24.

17 Anderson SL, Trujillo JM — Lixisenatide in type 2 diabetes: latest evidence and clinical usefulness. *Ther Adv Chronic Dis* 2016; **7(1):** 4-17. doi:10.1177/2040622315609312.

18 Raccah D, Lin J, Wang E, Germé M, Perfetti R, Bonadonna RC, *et al* — Once-daily prandial lixisenatide versus once-daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials. *J Diabetes Complications* 2014; **28(1):** 40-4.

19 Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V — Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). *Diabetes Care* 2015; **38(12):** 2241-9.

20 Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, *et al* — Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet* 2015; **385(9982):** 2057-66.

21 Courtney H, Nayar R, Rajeswaran C, Jandhyala R — Long-term management of type 2 diabetes with glucagon-like peptide-1 receptor agonists. *Diabetes Metab Syndr Obes* 2017; **10:** 79-87.

22 Porcellati F, Lucidi P, Bolli GB, Fanelli CG — GLP-1 RAs as compared to prandial insulin after failure of basal insulin in type 2 diabetes: lessons from the 4B and Get-Goal DUO2 trials. *Diabetes Metab* 2015; **41(6 Suppl 1):** 6S16-6S20.

23 Reid TS — Practical Use of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Primary Care. *Clin Diabetes* 2013; **31(4):** 148-57.

24 Maceira E, Lesar TS, Smith HS — Medication related nausea and vomiting in palliative medicine. *Ann Palliat Med* 2012; **1(2):** 161-76.

25 Raccah D, Bretzel RG, Owens D, Riddle M — When basal insulin therapy in type 2 diabetes mellitus is not enough–what next? *Diabetes Metab Res Rev* 2007; **23(4):** 257-64.

26 Verma S, Poulter NR, Bhatt DL, Bain SC, Buse JB, Leiter LA, *et al* — Effects of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke. *Circulation* 2018; **138(25):** 2884-94.

27 Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, *et al* — Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375(19):** 1834-44.

28 Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, *et al* — Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394(10193):** 121-30.

29 Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, *et al* — Diabetic kidney disease: a report from an ADA consensus conference. *Am J Kidney Dis* 2014; **64(4):** 510-33.

30 Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, *et al* — Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; **6(8):** 605-17.

Review Article

Reassuring the CV safety of Sulfonylureas : A Review article to readdress the CV safety of Modern Sulfonylureas post CAROLINA trial

B Krishnakumar[1], Priya Ann Sam[2]

For decades, sulfonylureas (SUs) have been important drugs in the antidiabetic therapeutic armamentarium. They have been used as monotherapy as well as combination therapy. Focus on newer drugs and concerns about the risk of severe hypoglycemia and weight gain with some SUs have led to discussion on their safety and utility. It has to be borne in mind that the adverse events associated with SUs should not be ascribed to the whole class, as many modern SUs, such as glimepiride and gliclazide modified release, are associated with better safety profiles. One such trial is the CAROLINA trial where the trial finally put concerns about sulfonylureas' cardiovascular safety to rest. Considering their efficacy, safety, pleiotropic benefits, and low cost of therapy, SUs should be considered as recommended therapy for the treatment of diabetes.

[*J Indian Med Assoc* 2019; **117(11)**: 23-5 & 29]

Key words **: CV safety, Sulfonylureas, Glimepiride.**

The type 2 diabetes mellitus (T2 DM) pandemic[1] is characterized by increasing complexity of management, raising concerns over safety and cost of therapy. Most guidelines state that metformin should be first-line therapy followed by various options for second-line treatment if sufficient glycemic control is not achieved after metforminmono therapy. Both dipeptidyl peptidase-4 (DPP-4) inhibitor and sulfonylureas are widely used second-line glucose-lowering agents. Sulfonylureas are used mainly based on their low cost, well-established glucose-lowering action, and a longstanding experience in clinical practice. However, sulfonylureas are associated with increased risk of hypoglycemia and modest weight gain[2].

Today, new diabetes agents face increased regulatory scrutiny and are required to demonstrate CV safety before, or after, approval. Indeed, the US Food and Drug Administration (FDA) key post-approval criterion to exclude unacceptable CVD risk for new diabetes drugs is an upper bound of the 95% confidence interval (CI) of <1.3 for the hazard ratio (HR) of CV events[3]. On the other hand, the regulatory requirements provided the opportunity for some of the drugs in CV outcome trials tested for CV benefits. This review covers the current evidence on the long-term risk of CV events with sulphonylureas (SUs), which remains one of the most widely used drug classes in T2 DM.

[1]DNB (Cardiology), Assistant Professor, Department of Cardiology, Government Medical College and Hospital, Trivandrum 695017

[2]MD (Pharmacology), Manager, Medical Services, Medical Affairs Division, Lupin Limited, Mumbai 400051 and Corresponding Author

Since SUs are still being advocated as second-line therapy added-on to metformin, as one of several classes, and in certain circumstances first-line therapy in T2 DM management, definitive data from a dedicated RCT addressing the CV safety question with SUs would be informative. Cardiovascular Outcome Study of Linagliptin *versus* Glimepiride in Patients with Type 2 Diabetes (CAROLINA) is such a trial, ongoing since November 2010, and is currently the largest head-to-head CV outcome trial that involves a comparison of a SU (glimepiride) with a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin) and provided a unique perspective with respect to CV outcomes with these two commonly used agents[2].

SUs are well-established glucose-lowering drugs, with insulinotropic action on pancreatic ß-cells. Since the introduction of tolbutamide in 1956[4], newer SUs have been developed, broadly classified based on their affinity to bind with sulfonylurea receptor (SUR) proteins[5]. The availability of modern SUs (glimepiride, glipizide, gliclazide MR and gliclazide modified release [MR]) with fewer side-effects and better efficacy[6] have contributed to their popularity.

SUs are insulin secretagogues that stimulate endogenous insulin secretion by blocking adenosine triphosphate-sensitive potassium channels (K_{ATP}) on pancreatic ß-cells, by binding to the SUR subunit present on the ß-cell plasma membrane[7]. SUs bind to a common SUR unit on ß-cells causing closure of the K_{ATP} channels and inhibition of K^+ efflux, consequently depolarising the membrane and facilitating influx of Ca^{+2} ions. This in turn

stimulates the exocytosis of insulin secretory vesicles[7]. Because insulin secretion is non-glucose-mediated, conventional SUs have been associated with a higher risk of hypoglycaemia.

All Sulfonylureas Are Not the Same :

SUs stimulate insulin secretion by blocking K_{ATP} channels in the pancreatic ß-cell membrane, by binding to the SUR subunit of the channel[8]. K_{ATP} channels are also present in extrapancreatic tissues, but often contain different types of SUR subunit. Evidence suggests that the effect of SUs on these K_{ATP} channels in different tissues varies[9]. For instance, gliclazide and tolbutamide block SUR_1 with higher affinity compared to SUR_2 while glibenclamide and glimepiride block both receptors with similar affinity.

Glimepiride stimulates insulin secretion by binding to a specific 65-kDa protein site on the K_{ATP} channel of pancreatic ß-cell and exerts allosteric inhibition of the SUR complex[10,11]. Further, compared to glibenclamide, glimepiride exhibits lower binding affinity (2- to 3-fold) for SUR as well as higher rate of association (2.5- to 3-fold) and dissociation (8- to 9-fold) from the receptor[10,12]. The distinct binding site and receptor interactions of glimepiride are believed to result in lower inhibition of K_{ATP} channel and hence, there is reduced risk of hypoglycaemia as compared to conventional SUs.

Variations in the pharmacodynamic/pharmacokinetic (PK/PD) profiles of individual SUs also explain the differences in anti-diabetic activity, hypoglycaemic risk, specificities to different tissue-specific SURs, effects on myocardial ischemic preconditioning, and insulin secretory effects[13]. In light of this, it may be wise to choose modern SUs that pose lower risk of hypoglycaemia and are cardiac friendly.

Cardiovascular Safety :

Concerns about the CV safety of SUs were raised initially in 1970s when the University Group Diabetes Program (UGDP) study found an increased association between tolbutamide use and risks of coronary artery events[14]. However, the UGDP suffers numerous flaws in the design, execution, analysis and interpretation of findings[15]. In fact, the UGDP findings prompted initiation of UKPDS, which found no detrimental effect of SUs on macrovascular complications or mortality in patients with T2DM[16]. This benefit persisted for up to 10 years in patients who had attained better glycaemic control. Similar results were observed from 15 well designed long term (≥72-weeks) RCTs, including ADOPT, ADVANCE and ADVANCE-ON, where treatment with SUs was not found to be associated with an increase in CVD risk or mortality[17].

Modern SUs (gliclazide MR and glimepiride) are associated with a lower risk of all-cause and CV-related mortality compared to conventional SUs in T2DM patients[18].

Ischemic Preconditioning :

Glibenclamide inhibited mitochondrial K_{ATP} channels, impaired IPC and increased experimental infarct size, whereas glimepiride did not inhibit beneficial effects of mitochondrial K_{ATP} channel opening and showed no adverse effect on IPC or infarct size[19]. Moreover glimepiride was found to maintain myocardial preconditioning with fewer CV side effects as compared to glibenclamide (P=0.01 *versus* P=0.34, respectively)[20]. Although both glibenclamide and glimepiride have affinity for the SUR2 receptor, glimepiride appears to preserve myocardial preconditioning, a property not shared by glibenclamide. Glimepiride was also reported to have a more rapid as well as longer duration of action; despite less stimulation of insulin secretion in comparison with glibenclamide[21]. Therefore, the effect of SUs on cardiac events depends on the molecule being used and the individual clinical setting of the individual case.

The CAROLINA Study :

In this long-term, multicenter, double-blind, randomized, active comparator trial of individuals with relatively early type2 diabetes at elevated cardiovascular risk, linagliptin was noninferior to glimepiride for the combined 3P-MACE end point. The current study demonstrates noninferior cardiovascular safety effects for linagliptin *versus* glimepiride when used predominantly as a second-line glucose-loweringtreatment option aftermetformin. CAROLINA is the first cardiovascular outcomes trial to include an active comparator and it provides valuable information about both linagliptin and glimepiride. It provides reassurance about the long-debated cardiovascular safety of sulfonylureas.

The new findings don't change current treatment recommendations for use of a type 2 diabetes agent with proven cardiovascular benefit — a sodium-glucose cotransporter type 2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) agonist — after metformin in patients with established cardiovascular disease.But for other patients with type 2 diabetes, SU is the choice of a second-line agent when cost is an issue[22].

CAROLINA involved 6033 individuals with type 2 diabetes from 607 sites in 43 countries[22]. All had relatively recent diabetes onset (median duration 6.3 years) and most had pre-existing cardiovascular disease (42%) or two or more defined cardiovascular risk factors (37%). Most (83%) were already taking metformin, but 9% were treatment naive at baseline. Those taking insulin were excluded. Over a median of 6.3 years — the longest cardiovascular outcomes

trial to date, note the researchers — there were no differences in the overall composite endpoint of cardiovascular death (fatal stroke and fatal myocardial infarction [MI]), nonfatal MI (excluding silent MI), or nonfatal stroke. Overall, the 3-point MACE occurred in 11.8% of the 3023 participants receiving linagliptin compared with 12.0% of the 3010 participants receiving glimepiride (hazard ratio [HR], 0.98; P = 0.7625)[22].

Similarly, nonsignificant differences were seen between linagliptin and glimepiride for each individual component of CV death (HR 1.00; 5.6% *versus* 5.6%; P = 0.9863), nonfatal MI (HR, 1.01; 4.8% *versus* 4.7%; P = 0.9060), and nonfatal stroke (HR, 0.87; 3.0% *versus* 3.5%; P = 0.3352)[22].

The same was true for secondary endpoints including hospitalization for heart failure (HR, 1.21; 3.7% *versus* 3.1%; P = 0.1761), CV death (HR, 1.00), non-CV death (HR, 0.82), and all-cause mortality (HR, 0.91)[22].

No differences were seen in glycemic control. HbA1c levels dropped more quickly with glimepiride, but by the end of the trial both groups had returned to a baseline of around 7.0%. There were no differences in the proportion of patients for whom new glucose-lowering therapies, including insulin, were required (about 40% in both groups).

Those in the glimepiride group initially gained about 0.6 kg in weight while the linagliptin group lost about 1.0 kg. By the end of the trial, the glimepiride group weighed about 1.5 kg more than the linagliptin participants.

No differences were seen between the groups in systolic or diastolic blood pressure, or in LDL cholesterol, HDL cholesterol, or triglycerides.

Hypoglycemia occurred significantly more often in the glimepiride group, including hypoglycemia overall (37.7% *versus* 10.6%; P<0.0001), moderate to severe hypoglycemia (30.9% *versus* 6.5%; P<0.0001), severe hypoglycemia (2.2% *versus* 0.3%; P<0.0001), and hospitalization due to hypoglycemia (0.9% *versus* 0.1%; P = 0.0004)[22].

Conclusion :

SUs are the main stream of pharmacotherapy in the management of patients with T2DM. Their well-established glycaemic efficacy, safety and tolerability support their use as an integral part of diabetes treatment. The CAROLINA trial addresses the sulfonylurea CV controversy. This reaffirms current clinical recommendations to choose Glimepiride after Metformin based on proven CV benefits and cost factor. CV safety should no longer be a consideration in the decision making process for selecting Glimepiride with other modern SU. Given the fact that many of the clinical concerns associated with the use of SUs are agent-specific, and do not pertain to the class as such, a careful choice of specific SU should be considered beneficial. Considering better glycaemic efficacy, long-term outcomes and low medication cost, SUs, should be continued to be used as a front-line agent in the treatment algorithm of T2DM, particularly in India. Proper patient selection, choice of drug and dose, patient education and empowerment, and physician training will help ensure effective and safe use of this important class of drugs.

References

1 International Diabetes Federation. Key Findings. 2014. [Last accessed on 2015 Mar 25]. Available from: http://www.idf.org/diabetesatlas/update-2014

2 Das SR, Everett BM, Birtcher KK — 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018; **72(24):** 3200-23.

3 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetes therapies to treat type 2 diabetes, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf (2008)

4 Seltzer HS — Efficacy and safety of oral hypoglycemic agents. *Annu Rev Med* 1980; **31:** 261-72.

5 Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JP 4th, Boyd AE 3rd, González G, *et al* — Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science* 1995; **268(5209):** 423-6.

6 Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens R — Diabetologia Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. 2013; **56(5):** 973-84.

7 Kramer W, Müller G, Geisen K — Characterization of the molecular mode of action of the sulfonylurea, glimepiride, at beta-cells. *Horm Metab Res* 1996; **28(9):** 464-8.

8 Gribble FM, Reimann F — Differential selectivity of insulin secretagogues: mechanisms, clinical implications, and drug interactions. *J Diabetes Complications* 2003; **17(2 Suppl):** 11-5.

9 Ashcroft FM, Gribble FM — Tissue-specific effects of sulfonylureas: lessons from studies of cloned K(ATP) channels. *J Diabetes Complications* 2000; **14(4):** 192-6.

10 Briscoe VJ, Griffith ML, Davis SN — The role of glimepiride in the treatment of type 2 diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2010; **6(2):** 225-35.

11 Müller G, Hartz D, Pünter J, Okonomopulos R, Kramer W — Differential interaction of glimepiride and glibenclamide with the beta-cell sulfonylurea receptor. I. Binding characteristics. *Biochim Biophys Acta* 1994; **1191(2):** 267-77.

12 Holstein A, Plaschke A, Egberts EH — Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev* 2001; **17(6):** 467-73.

(Continued on page 29)

Original Article

Assessment of Relationship between Tumour Thickness and Nodal Metastasis in Head and Neck Squamous Cell Carcinoma

Deepak K Gupta[1], Saurabh Makkar[2], Neena Chaudhary[3], Rekha Sevda[4]

The present study was undertaken to assess the relationship between tumour thickness and nodal metastasis in head and neck squamous cell carcinoma, with an idea in mind to improvise the treatment for these cancer further. In our study, 40 patients with proven head and neck squamous cell cancer and requiring surgery as primary mode of treatment were included in study. All patients underwent neck dissection along with surgical treatment for the primary tumour. Specimen of neck dissection was sent for histopathological examination. The pathologist examined the tumour thickness and lymph node metastasis. Statistical Package for the Social Sciences (SPSS) 17.0 used and categorical variables are presented as absolute numbers and percentage and were compared using Chi-squared test or Fisher's exact test as appropriate. P value <0.05 was considered statistically significant. In our study of 40 patients, a significant correlation between pathological lymph node metastasis and tumour thickness with p value is of 0.001. Out of 19 oral cancer patients and 21 laryngeal cancer patients, a significant correlation was found between pathological lymph node metastasis and tumour thickness with a 'p' value of 0.023 and 0.02 respectively. Cut-off value for tumour thickness was kept at 7mm.

Tumour thickness gives an accurate estimate of tumour load and it could guide in adjuvant treatment for regional lymph nodes. Elective neck dissection can be avoided in patients with limited tumour thickness but close postoperative follow up is required.

[*J Indian Med Assoc* 2019; **117(11):** 26-9]

Key words **: Tumour thickness, Nodal metastasis, Elective neck dissection.**

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer worldwide. The annual incidence of head and neck cancers worldwide is more than 5,50,000 cases with around 3,00,000 deaths each year[1]. Overall 57.5% of head and neck squamous cell carcinoma occur in Asia, especially, India where it is the most common cancer[2]. In India, HNSCC accounts for 30% of all cancers[3].

HNSCC includes epithelial cancers arising in the mucosa of the upper aero-digestive tract which include the oral cavity, oropharynx, hypopharynx and larynx. These cancers are strongly associated with certain environmental and lifestyle risk factors like smoking, tobacco chewing, alcohol and also related to several strains of human papilloma virus (HPV 16, 18)[4].

Tumour thickness is a parameter that indicates aggressiveness of a tumour. It is defined as tumour mass that reveals the vertical growth capacity of the tumour. Tumour cells with a greater malignant potential are prone to break through these protective barriers and invade vertically. Horizontal spread, on the other hand, occurs in superficial lesions that are under the control of body resistance[5,6]. Accurate prediction of histological tumour thickness may influence management regarding surgical access, planned margins, use of reconstruction and elective neck dissection.

Tumour thickness has been shown to be one of the most important and reliable factor in predicting regional node involvement in oral cavity cancers[7]. It is now widely accepted that thickness is more accurate predictor of sub-clinical nodal metastasis, local recurrence and survival than tumour size[6].Tumour thickness can be measured pre-operatively by intraoral ultrasonography, high resolution CT or MRI. It can be measured post-operatively from the specimen or by frozen section intraoperatively.

Regional lymph node metastasis is a well-known prognostic indicator in many types of solid cancer, including HNSCC[8]. Lymph node metastasis negatively influences the overall survival and increases the likelihood of distant metastases.

Elective neck dissection gives an important pathologic information on the status of lymph node metastasis and

Department of ENT, VMMC and Safdarjung Hospital, New Delhi 110029

[1]MS (ENT), Assistant Professor

[2]MS (ENT), DNB (ENT), Senior Resident and Corresponding Author

[3]MS (ENT), Professor

[4]MBBS, Ex Intern, Lady Hardinge Medical College, New Delhi 110001

helps to determine need for chemo-radiation. It also clears pathologically undetectable cancer cells lodged in the lymphatics between the primary tumour and the echelon lymph nodes. Shunting of lymph with opening up of abnormal channels occurs when more extensive surgery and radiotherapy is undertaken. Hence, it is important to assess tumour thickness with nodal metastasis, so that a proper treatment plan can be made according to the thickness of tumour to avoid morbidity and more extensive procedures to the patient.

In present study, we aim to assess the relationship of tumour thickness in head and neck squamous cell carcinoma to lymph node metastasis.

Materials and Methods

This study was conducted in Department of Otorhinolaryngology, Head and Neck Surgery, Safdarjung Hospital and National Institute of Pathology, New Delhi in 18 months of study period from October 2013 to March 2015.

A cross sectional study of 40 patients attending Outpatient Department of Otorhinolaryngology with proven head and neck squamous cell cancer and requiring surgery as primary mode of treatment were included in the study. Patients were divided into two groups of laryngeal cancer and oral cancer. Patients included were of any age group and both sexes.

A detailed relevant history was taken followed by a thorough general physical and otorhinolaryngological examination. Neck of patients was thoroughly examined for any palpable lymph nodes. Complete assessment of site, size and extent of primary tumour was done to properly stage the tumour. Patients were taken for haematological investigations, chest x-ray and ultrasound abdomen was done for patients to rule out any metastasis in lungs and abdomen. After clinical examinations all the patients were sent for ultrasound neck, contrast enhanced computed tomography-base of skull to thoracic inlet. Biopsy was taken from site of primary tumour in every patient for histopathological confirmation, degree of differentiation, and histological grading of malignancy.

All patients under study underwent neck dissection along with surgical treatment for the primary tumour. Specimen of neck dissection was sent for histopathological examination. The pathologist examined the tumour thickness and lymph node metastasis. The pathologist was blindfolded about the report of clinical examination and contrast enhanced computed tomography.

Statistical Analysis :

Statistical testing was conducted with the statistical package SPSS 17.0. Categorical variables are presented as absolute numbers and percentage and were compared using Chi-squared test or Fisher's exact test as appropriate. P value <0.05 was considered statistically significant.

Results

In our study group, patients ranged from 26-70 years of age with majority of patients in age group of 51-70 (58%). The mean age of patients was 53.3 years (Table 1).

There were 21 patients of laryngeal cancer (52.5%) and 19 patients of oral cancer (47.5%). Out of 19 laryngeal cancer patients, 12 (30%) patients had supraglottic cancer, 2(5%) patients had glottic cancer, 4(10%) patients had transglottic cancer and 3(7.5%) patients had hypopharyngeal cancer. Out of 19 oral cancer patients, 10(25%) patients had buccal mucosa cancer and 9(22.5%) patients had tongue cancer. In our study, the most common site for primary tumour was supraglottis ie, 30% (Table 2).

Table 1

Age group (years)	No of patients (Percentage)
10-30	2 (5%)
31-50	15 (37.5%)
51-70	23 (57.5%)

In our study group of 40 patients, 13 patients (32.5%) had tumour thickness ≤7mm and 27 patients (77.5%) had tumour thickness of >7mm. Of total 19 oral cancer patients, 9 patients (47.4%) had tumour thickness ≤7mm, 10 patients (52.6%) had tumour thickness of >7mm. Of total 21 laryngeal cancer patients, 4 patients (19%) had tumour thickness ≤7mm, 17 patients (81%) had tumour thickness of >7mm (Table 3).

Table 2

Primary site	No of patients (Percentage)
Oral	19 (47.5%)
Larynx	21 (52.5%)
Total	40 (100%)

We have compiled pathological lymph node metastasis into 2 groups as positive (N+) and negative (N-). Out of 40 patients, there were 22 patients (55%) in N+ group and 18 patients (45%) in N- group. Among 22 patients of N+ group, 2 patients (9.1%) were having tumour thickness ≤7mm and 20 patients (90.9%) were having tumour thickness >7mm. Among 18 patients of N- group, 11 patients (61.1%) were having tumour thickness ≤7mm, 7 patients (38.9%) were having tumour thickness >7mm. Association of tumour thickness with pathological lymph node metastasis in head and neck cancers were statistically significant (p<0.001).

Table 3

Site	Tumour thickness	Tumour thickness >7mm	Total
Oral	9 (47.4%)	10 (52.6%)	19
Larynx	4 (19%)	17 (81%)	21

There were no cases of N+ among laryngeal cancer patients with tumour thickness less than 7mm. The result was similarly statistically significant for both oral and laryngeal cancers separately (Table 4).

Discussion

Head and neck squamous cell cancers themselves represent a fairly heterogeneous group of cancers with

Table 4

Pathological Ln Metastasis	Tumour Thickness ≤7mm Frequency (%)	Tumour Thickness >7mm Frequency (%)	P-value
Overall :			
Negative	11 (84.6%)	7 (25.9%)	
Positive	2 (15.4%)	20 (74.1%)	<0.001
Total	13 (100.0%)	27 (100.0%)	
Oral :			
Negative	7 (77.8%)	2 (20.0%)	
Positive	2 (22.2%)	8 (80.0%)	0.023
Total	9 (100.0%)	10 (100.0%)	
Larynx :			
Negative	4 (100.0%)	5 (29.4%)	
Positive	0 (0%)	12 (70.6%)	0.02
Total	4 (100.0%)	17 (100.0%)	

different demands for preservation of cosmetic and functional needs as dictated by their anatomical sites, unequal response to treatment protocols, and variable prognosis. In the last decade, studies have provided increased insight in the molecular and genetic changes that are responsible for the development of cancer and the biologic behaviour of cancer cells.

Tumour thickness is a relatively new prognostic factor that has been investigated for head and neck cancers. TNM classification does not represent the real tumour load but integrated classification, which includes use of tumour thickness, can be used to overcome the well-known lack of consistency in the choice of treatment which can eventually improve overall survival. Tumour thickness adds another dimension to the staging system. Although several studies[5,10,11] have considered tumour thickness and tumour depth synonymous, they are different and should be distinguished. The tumour thickness refers to the thickness of the entire tumour mass, whereas the tumour depth is the extent of tumour growth into the tissue beneath the epithelial surface.

Nodal disease demonstrates a major problem in deteriorating survival and highlights the importance of accurate diagnosis and therapeutic control[12]. The anatomical characteristics and biological behaviour of the primary tumour are the main determinants of the cervical nodal status.

In the present study of 40 patients, majority of them ranged between 51-70 years (57.5%) & the mean age of patients was found to be 53.3 years and there was marked male preponderance with male female ratio of 9:1.

In our study of 40 patients, a significant correlation between pathological lymph node metastasis and tumour thickness with p value of 0.001. Various studies[13-15] in literature reported a significant correlation between pathological lymph node metastasis and tumour thickness & have shown that elective neck dissection should be done if tumour thickness is more than cut-off value, even in clinically N0 patients.

Out of 19 oral cancer patients and 21 laryngeal cancer patients, a significant correlation was found between pathological lymph node metastasis and tumour thickness with a 'p' value of 0.023 and 0.02 respectively. Hu *et al*[13] evaluated 223 patients with oral tongue squamous cell carcinoma and showed a significant correlation between pathological lymph node metastasis and tumour thickness. Melchers *et al*[14] evaluated 212 oral cancer patients and Ganly *et al*[15] evaluated 164 oral cancer patients and reported a significant correlation between pathological lymph node metastasis and tumour thickness. Yilmaz *et al*[16] reported a significant correlation between pathological lymph node metastasis and tumour thickness among 111 laryngeal cancer patients. Ye *et al*[17] evaluated 127 patients with supraglottic and hypopharyngeal cancer and found that tumour depth provides additional information in an effort to predict nodal status.

The results of our study were in accordance with previous studies. However, there were few limitations in our study. Multiple tumour thickness cut-offs could have been taken to get an accurate idea of nodal metastasis at particular cut-off. But, in previous studies, cut-off point varied greatly and our sample size was limited which suggests the need for a larger prospective study to get more accurate results.

Conclusion

In our study, it was found that tumour thickness >7mm lead to significant increase in nodal metastasis. Tumour thickness, 3rd dimension of tumour, has a significant impact on nodal metastasis in Head and Neck Squamous Cell Carcinoma as it gives an accurate estimate of tumour load and it could guide in adjuvant treatment for regional lymph nodes. Elective neck dissection can be avoided in patients with limited tumour thickness but close postoperative follow up is required. Further studies with larger sample size are required to understand the intricate mechanism of nodal metastasis and its relation with tumour thickness which leads to more rational treatment in HNSCC.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D — Global cancer statistics. *CA Cancer J Clin* 2011; **61(2):** 69-90.

2 Trivedi NP, Kekatpure VD, Trivedi NN, Kuriakose MA — Head and neck cancer in India: Need to formulate uniform national treatment guideline? *Indian J Cancer* 2012; **49(1):** 6-10.

3 Kulkarni MR — Head and neck cancer burden in India. *Int J Head and Neck Surg* 2013; **4(1):** 29-35.

4 Kreimer AR, Clifford GM, Boyle P, Franceschi S — Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systematic review. *Cancer Epidemiol Biomarkers Prev* 2005; **14(2):** 467-75.

5 Moore C, Kuhns JG, Greenberg RA — Thickness as

prognostic aid in upper aerodigestive tract cancer. *Arch Surg* 1986; **121(12):** 1410-4.
6 Clark WH Jr, From L, Bernardino EA, Mihm MC — The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969; **29(3):** 705-27.
7 Pentenero M, Gandolfo S, Carrozzo M — Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck* 2005; **27(12):** 1080-91.
8 Woolgar JA — Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. *Oral Oncol* 2006; **42(3):** 229-39.
9 Edge SB, Compton CC — The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17(6):** 1471-4.
10 Jang JY, Kim MJ, Ryu G, Choi N, Ko YH, Jeong HS — Prediction of lymph node metastasis by tumor dimension versus tumor biological properties in head and neck squamous cell carcinomas. *Cancer Res Treat* 2016; **48(1):** 54-62.
11 Taniguchi M, Watanabe A, Tsujie H, Tomiyama T, Fujita M, Hosokawa M, *et al* — Predictors of cervical lymph node involvement in patients with pharyngeal carcinoma undergoing endoscopic mucosal resection. *Auris Nasus Larynx* 2011; **38(6):** 710-7.
12 Prades JM, Timoshenko AP, Schmitt TH — Planned neck dissection before combined chemoradiation for pyriform sinus carcinoma. *Acta Otolaryngol* 2008; **128(3):** 324-8.
13 Hu H, Cheng KL, Xu XQ, Wu FY, Tyan YS, Tsai CH, *et al* — Predicting the Prognosis of Oral Tongue Carcinoma Using a Simple Quantitative Measurement Based on Preoperative MR Imaging: Tumor Thickness versus Tumor Volume. *AJNR Am J Neuroradiol* 2015; **36(7):** 1338-42.
14 Melchers LJ, Schuuring E, van Dijk BA, de Bock GH, Witjes MJ, van der Laan BF, *et al* — Tumour infiltration depth ≥4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. *Oral Oncol* 2012; **48(4):** 337-42.
15 Ganly I, Goldstein D, Carlson DL, Patel SG, O'Sullivan B, Lee N, *et al* — Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumour thickness. *Cancer* 2013; **119(6):** 1168-76.
16 Ye LL, Jia R, Xing WF, Kong FF, Hu CS, Hong MY — The prognostic value of tumor depth for cervical lymph node metastasis in hypopharyngeal and supraglottic carcinomas. *Head & Neck* 2019; **41(7):** 2116-22.

(Continued from page 25)

13 Proks P, Reimann F, Green N, Gribble F, Ashcroft F — Sulfonylurea stimulation of insulin secretion. *Diabetes* 2002; **51 Suppl 3:** S368-76.
14 Feinglos MN, Bethel MA — Therapy of type 2 diabetes, cardiovascular death, and the UGDP. *Am Heart J* 1999; **138(5 Pt 1):** S346-52.
15 A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). *Seltzer HS Diabetes* 1972; **21(9):** 976-9.
16 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352(9131):** 837-53.
17 Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, *et al* — Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res* 2013; **10(4):** 289-301.
18 Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR — Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3(1):** 43-51.
19 Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM — Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* 2001; **103(25):** 3111-6.
20 Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, *et al* — Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20(6):** 439-46.
21 Raptis SA, Hatziagelaki E, Dimitriadis G, Draeger KE, Pfeiffer C, Raptis AE — Comparative effects of glimepiride and glibenclamide on blood glucose, C-peptide and insulin concentrations in the fasting and postprandial state in normal man. *Exp Clin Endocrinol Diabetes* 1999; **107(6):** 350-5.
22 Rosenstock J, Kahn S, Johansen O, Zinman B, Espeland M, Woerle H, *et al* — Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes. *JAMA* 2019; **322(12):** 1155.

Original Article

Prevalence of Periodontal diseases in Type 2 Diabetes

Aakansha Malawat[1], Pampita Chakraborty[2], Pradip Mukhopadhyay[3], Kingshuk Bhattacharjee[4], Abhijit Chakraborty[5], Sujoy Ghosh[6]

Periodontal disease is a less recognised, but well documented complication of diabetes mellitus. In this study we evaluated the prevalence of periodontal disease in Type 2 Diabetes Mellitus (DM). Four hundred and twelve subjects with type 2 diabetes were evaluated for periodontal status. Community Periodontal Index (CPI) modified, Simplified Oral Hygiene Index (OHI-S) and Mobility was assessed in all. The prevalence of periodontal diseases in Type 2 diabetic patients was 61.9%. Bleeding on probing was present in 90% of the subjects, pocket probing depth in 59.5% and loss of attachment in 61.9%, indicating periodontal diseases, a frequent and severe complication in type 2 diabetes. Subjects with type 2 DM have a high prevalence and severe form of periodontal disease.

[*J Indian Med Assoc* 2019; **117(11):** 30-2 & 35]

Key words **: Prevalence, periodontal disease, Community periodontal index, type 2 diabetes mellitus.**

Diabetes mellitus is a complex and globally evolving chronic health problem faced by the world today. The total number of people in the world with diabetes is expected to rise from 171 million in 2000 to 366 million in 2030[1]. Periodontal diseases are the most common diseases that includes gingivitis or periodontitis. In periodontitis, the primary etiologic factor may be microbiologic, systemic, or physical injury. The signs and symptoms are gingival bleeding, increase in pocket probing depth, destruction of periodontal attachment (mainly, bone) and tooth loss[2]. It is best considered as the outcome of an ongoing host-parasite interaction between pathogenic microorganism that colonized in the periodontal pocket and host tissues that resist such bacteria or their products. Inadequate antimicrobial defence strategies of the host frequently result in the loss of normal structural components such as collagen fibres of gingival and periodontal ligament and replacement of these fibres by dense infiltrates of the inflammatory mediators[3].

Recently, much emphasis has been laid down to potentiate the impact of systemic disease on the oral health. Various systemic diseases and disorders are considered as risk factors of periodontal diseases. One such example is diabetes mellitus[4].

As per Loe[7], periodontal diseases are considered as the 6th complication of diabetes. Chronic, gram negative periodontal infection is currently thought to increase insulin resistance, contributing to the development of metabolic imbalance and thus destabilizes the glycemic status of the person with diabetes[5].

In a study by Almas *et al*, at the King Saud University, College of Dentistry, evaluated 40 subjects for periodontal health, 20 in each group of healthy and diabetic subjects, with ages ranging from 20 to 70 years. It was observed that the severity of periodontal disease increased with the increase in the blood glucose level. There was a steady increase in blood glucose level with increase in Community Periodontal Index of Treatment Needs (CPITN) scores[6]. CPITN is an epidemiological screening procedure for periodontal treatment needs in populations and also, in a modified form for screening and monitoring of individuals by dental practitioners. A cross-sectional study was conducted to determine the relationship between DM and oral health status in Pima Indians from the Gila River Indian community in Arizona by Emrich *et al*. The findings of their study demonstrated that diabetes increases the risk of developing destructive periodontal disease about threefold[7].

In this background, we have evaluated the prevalence of periodontal disease in Type 2 Diabetes Mellitus in an Indian context.

Materials and Methods

The present study is a descriptive cross-sectional study, carried out to assess the prevalence of periodontal diseases in patients with Type 2 DM. A total of 412 consecutive adults aged between 25-75 years diagnosed with Type 2 Diabetes Mellitus attending the dedicated

[1]Final Year Postgraduate Trainee, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, Kolkata 700114

[2]PhD Research Fellow, Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education & Research, Kolkata 700020 and Corresponding Author

[3]MD, DM (Endo), Associate Professor, Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education & Research, Kolkata 700020

[4]PhD Scholar, Department of Medical Sciences, JJT University, Rajasthan 333001

[5]MDS, HOD, Professor, Department of Periodontology, Guru Nanak Institute of Dental Sciences and Research, Kolkata 700114

[6]MD (Med) DM (Endocrinology) FRCP FICP, Associate Professor, Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education & Research, Kolkata 700020

AMRI Institute of Diabetes and Hormonal Disorders, Kolkata were recruited. Duration of diabetes and history of addiction was documented in all.

AMRI Institute of Diabetes and Hormonal Disorders, Kolkata was selected as the patients who visit the center belong to higher socio-economic status so as to remove the effect of chronic malnourishment on dental health and lack of knowledge about oral hygiene. It is a well-established center for treatment of diabetes patients with a dedicated team of endocrinologists, ophthalmologists, dentists and diabetic educator who work together to provide patients with advance care and management of complex endocrine disorders.

The study protocol was explained to each potential subject and written informed consent was obtained prior to the commencement of the study. Ethical clearance was obtained from the research review board committee of AMRI Institute of Diabetes and Hormonal Disorders, Kolkata.

The subjects were diagnosed to have diabetes according to American Diabetes Association criteria 2018.

- A fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L), or
- A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) or
- HbA1c ≥6.5% (48mmol/mol)

Inclusion Criteria :

- Subjects of both sexes previously diagnosed with Type 2 diabetes
- Subjects were aged between 25-75 years
- Subjects with minimum 20 permanent teeth

Exclusion Criteria :

- Subjects suffering from Type 1 Diabetes Mellitus
- Those with other chronic diseases and on medications that could influence the oral health status.
- Subjects with less than 20 permanent teeth
- Current smokers or ex-smokers for four to six month
- Unable to cooperate due to their physical or mental status.

Periodontal Assessment : The periodontal examination was based on Simplified Oral Hygiene Index (OHI-S), Community Periodontal Index (CPI) modified and mobility. All assessments were performed by 1 of 2 trained examiners using a Shepherd Hook Explorer and WHO periodontal probe to determine the parameters.

OHI-S, which includes the Debris and Calculus index were employed for assessing the oral hygiene condition of the subjects[8]. Community Periodontal Index (CPI) modified consists of the following components, which are scored separately: Gingival bleeding and periodontal pocket depth. Bleeding on Probing (BOP) helps to assess periodontal status of subjects. Bleeding after stimulation is indicative of inflammation or erosion in gingival sulcus[9,10]. BOP is recorded as present or absent within 30 seconds after probing. Probing Pocket Depth (PPD) defined "as the distance between the gingival margin and the bottom end of the periodontal pocket"[11] was measured by a specially designed, lightweight CPI metallic probe with a 0.5 mm ball tip, black band between 3.5 and 5.5 mm, and rings at 8.5 and 11.5 mm from the ball tip. All teeth present in the mouth are examined for absence or presence of gingival bleeding and periodontal pockets. Loss of Attachment (LOA) is recorded. It represents the distance from Cemento-Enamel Junction (CEJ) to the bottom of periodontal pocket. For loss of attachment, only 10 teeth known as index teeth are examined for an epidemiological survey. The teeth have been identified as the best estimate of the worst periodontal condition of the mouth[12].

According to the Canadian Health Measures Survey 2007-2009, the measurement of loss of periodontal ligament attachment is considered the gold standard in reporting the prevalence of periodontal disease[13]. National Health and Nutrition Examination Survey (NHANES) determined the attachment loss and Pocket Probing depth at six sites of all teeth (excluding third molars) for the estimation of periodontal disease in the US[14].

Based on the above parameters, periodontal diseases were diagnosed as having presence of bleeding on probing (BOP) or a probing pocket depth (PPD) measuremrnt of more than 4 mm, or loss of attachment (LOA) of more than 4 mm or any combinations of these parameters.

Statistical Analysis : Descriptive statistical analysis was carried out with Statistical Package for Social Sciences Version 21.0 for windows (SPSS Inc, Chicago, IL, USA) with Microsoft Word and Excel being used to generate tables.

Results on continuous measurements are presented as mean ±SD and results on categorical measurements are presented in percentage. Statistical significance is assessed at a level of 5%. Normality of data was tested by Kolmogorov-Smirnoff test and visually by QQ plot.

Results : Out of the total 412 participants included in the study, 235(57%) were male and 177(43%) were female. The age of the participants ranged between 25 to 78 years with a mean age of 54.17 (±10.58) years. The mean duration of type 2 diabetes is 8.53 (±4.78) years. The mean of the glycemic parameters, fasting blood sugar (FBS), postprandial blood sugar (PPBS) and glycated hemoglobin (HbA1c) are 153.88mg/dl (±59.70), 216.11mg/dl (±88.06) and 7.95% (±2.02) respectively. These baseline features are shown in Table 1.

Among 412 participants, 157(38.1%) have mild Loss of attachment (LOA) (0-3mm), 250 (60.7%) have moderate LOA (4-5mm) and 5 (1.2%) subjects have severe LOA (6-8mm). Periodontal pocket depth was absent in 167 (40.5%) individuals. PPD was present in 245 participants, among which 238 (57.8%) had 4-5mm depth while 7(1.7%) had 6mm or more pocket depth. Two hundred and sixty-six subjects (64.56%) had poor oral hygiene, 137 (33.25%) had fair oral hygiene and only 9 (2.18%) had good oral hygiene. These

features are shown in Table 2.

About 371 (90%) participants had a tendency of gingival bleeding on probing (BOP) while only 41(10%) did not have positive BOP. Two hundred and forty-five (59.5%) subjects reported with no mobility of teeth while 167(40.5%) subjects had mobile teeth at the periodontal examination .These features are shown in Table 3.

Based on the above parameters, the prevalence of periodontal diseases in Type 2 diabetic patients is 61.9%.

Table 1 — *Baseline features of the participants (n=412)*

Parameters	Mean ± SD
Age (Years)	54.17±10.587
Duration of DM	8.53±4.78
Number of teeth present	28.89±2.42
Fasting Blood Sugar (FBS, mg%)	153.88±59.701
Post Prandial (PPBG mg%)	216.11±88.063
HbA1c(%)	7.95±2.027

Discussion

Sheridan *et al*, found that prevalence and severity of periodontal diseases increases with advancing age[15]. These findings could be due to deterioration of immune function and tissue integrity in older age that may increase the vulnerability to periodontal diseases. The present study also demonstrated that, there is a high prevalence of periodontal diseases in the elderly population.

Emrich et al stated that the duration of diabetes was strongly correlated to both prevalence and severity of periodontal diseases[7]. The present study also demonstrated that the prevalence rate of periodontitis is high in association with longer the duration, and poorer the control of diabetes mellitus.

Casarin RC et al, compared, subgingival plaque samples obtained from 71 type 2 diabetic patients with samples from healthy individuals. P. gingivalis, which is the main causative organism of periodontal destruction, was present in greater concentration in Type 2 diabetic patients. This study demonstrated that subjects with type 2 diabetes suffer from periodontal infection to a great extent[16].

In the present study, a significant majority of participants (266 out of 412) (64.56%) had poor oral hygiene with mean HbA1c of 7.95%. This finding may suggest that patients diagnosed with type 2 diabetes and having sub-optimal or poor glycemic control may have greater tendency of accumulations of plaque and calculus leading to more pronounce periodontal inflammation compared to healthy individuals.

Table 2 — *Periodontal Examination findings of the participants (n=412)*

Parameters	Number of subjects	Percent (%)
Loss of Attachment :		
0-3 mm	157	38.1
4-5 mm	250	60.7
6-8 mm	5	1.2
Pocket Depth :		
No pocket	167	40.5
4-5 mm	238	57.8
6 mm or more	7	1.7
OHIS :		
Good	9	2.18
Fair	137	33.25
Poor	266	64.56
PPD (Overall)	245	59.5
Periodontal Disease (Overall)	255	61.9

Table 3 — *Other Periodontal Examination findings of the participants (n=412)*

Parameters	Nil	Yes	Total
Mobility	245 (59.5%)	167 (40.5%)	412
Bleeding on probing	41 (10%)	371 (90%)	412

In this study, the index used for assessing the periodontal status of the population was modified CPI index. It is an ideal index for epidemiological studies because it uses accepted clinical criteria, full mouth scoring and a simple recording procedure, which allows rapid assessment of individuals for periodontal conditions related to treatment needs[17].

In periodontal diseases, gingival bleeding is one of the signs of acute gingival conditions. In this study, 90% of subjects with Type 2 DM have bleeding on probing. A 5-year follow-up study by Costa et al, demonstrated that periodontal tissue destruction is associated with poor glycemic control (HbA1c ≥6.5%)[18].

Similarly, the present study suggests that type 2 diabetes is associated with a high prevalence of periodontitis.

Thus, there is a high prevalence rate of periodontal diseases in Type 2 diabetic patients. An increase in the periodontal parameters is associated with high values of indices of glycemic control.

Conclusion :

Abnormal increase in the periodontal parameters is related with poor glycemic control. The present study also demonstrated an increased prevalence of periodontal diseases in subjects with Type 2 Diabetes Mellitus. It is necessary to maintain oral hygiene regularly and educate the patients to ensure there is change of lifestyle modifications and attitude so that they can go for regular dental check-ups for glycemic control and reduce the incidence of periodontal diseases in Type 2 Diabetes Mellitus.

References

1 Nicki R — Colledge: Davidson's principles and practice of medicine ELBS. Vol. 17. Philadelphia: Churchill Livingstone 1995; 669-774.

2 Serio FG, Howley CE — Etiology and classification of the periodontal diseases. Manual of clinical periodontics. 2nd ed, Lexi Comp, 2006, 22-30.

3 Grant DA, Stem IB, Listgarten MA — Periodontal health and disease. *Periodontics in the tradition of Gottlieb and Orban* 6th ed, The CV Mosby, 1988, 3-22.

4 Klokkevold PR, Mealey BL — Influence of systemic disorders and stress on the periodontium (Cited from: Newman MG, Takei HH, Klokkevold PR, Carranza FA: Clinical Periodontology. 10th ed, Elsevier, 2007, 284-311.

5 Loe H — Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993; **16(1):** 329-34.

6 Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J, Sardo,

(Continued on page 35)

Original Article

A study to compare the metabolic health (anthropologic and biochemical) between Scheduled Tribe and non-Scheduled Tribe population in underdeveloped parts in the District of Birbhum, West Bengal : A population based observational study

Rana Bhattacharjee[1], Dibakar Biswas[2], Kaushik Pandit[3], Purushottam Chatterjee[4], Subhankar Chowdhury[5], Sujoy Ghosh[6], Pradip Mukhopadhyay[7]

Metabolic disorders are common in India. There is paucity of data regarding metabolic health from the socio-economically backward population. This population based cross-sectional observational study was designed to assess the metabolic health related parameters in tribal population (STs) from a rural area in the district of Birbhum, West Bengal, India and compare them with non-tribal population (non-STs) from the same area. Various anthropometric parameters like height, weight, BMI, and waist circumference were recorded. Biochemical parameters like fasting plasma glucose, HbA1c, HOMA-IR, lipid profile, liver enzymes, uric acid, thyroid function test, calcium, phosphorus, 25 OH vitamin D, and iPTH were measured. Anthropologic and biochemical parameters were compared between STs and non-STs. Prevalence of obesity, diabetes, dyslipidemia and metabolic syndrome was significantly lower, whereas 25 OH vitamin D level was higher in Scheduled tribes comparison to non-Scheduled tribes.

[*J Indian Med Assoc* 2019; **117(11):** 33-5]

Key words **: Scheduled tribe, Metabolic health.**

Indians are predisposed to diabetes mellitus and other metabolic morbidities[1]. Prevalence of Metabolic Syndrome (MetS) in Asian Indians varies according to region, lifestyle patterns and other socioeconomic or cultural factors. Community based health studies are immensely important in understanding the metabolic disorders and associated cardiovascular risk factors. A high proportion of people in India including West Bengal belong to underdeveloped community. Though metabolic morbidities are very common across the country, no data regarding the metabolic health parameters of tribal and other backward populations from poorly developed areas are available from any large-scale study. This study aims to estimate the prevalence of obesity, insulin resistance, diabetes, hypertension, elevated liver enzyme, hyperuricemia, vitamin D deficiency, and thyroid dysfunction in a tribal population from the district of Birbhum in West Bengal as well as to compare those parameters with non-tribal population from the same area.

Department of Endocrinology and Metabolism, IPGME&R and SSKM, Kolkata 700020

[1]MD (Med), DM (Endocrinology), MRCP, FICP, Assistant Professor

[2]MD (Med), DM (Endocrinology), Assistant Professor and Corresponding Authors

[3]MD, DNB, DM (Endocrinology), Chief Consultant Endocrinologist, Belle Vue Clinic, Kolkata 700017

[4]MD, DM (Endocrinology), Consultant Endocrinologist, Apollo Gleneagles Hospital, Kolkata 700054

[5]MD (Med) DM (Endocrinology), MRCP, Professor & Head

[6]MD (Med) DM (Endocrinology) FRCP FICP, Associate Professor

[7]MD (Med) DM (Endocrinology), Associate Professor

Materials and Methods

Population :

We undertook a population based observational study for assessing the metabolic health (anthropologic and biochemical) of Scheduled Tribe (ST) population [Article 366 (25) and Article 342 of Constitution of India] and non-Scheduled Tribe population in underdeveloped rural areas in the District of Birbhum, West Bengal, India.

An awareness program was conducted in the selected areas by doing sensitization camp at every 2-3 months. This has been done with the help of Rural Extension Centre, Viswa Bharati, Birbhum, India. Then a simple questionnaire was administered for assessing the awareness about metabolic health especially those related to diabetes and other metabolic problems. A composite scoring was done for overall analysis of awareness. The persons were explained about the study and only those who gave informed written consent had been included in the final study.

All adult males and females giving consent and having no definite documented chronic infective or inflammatory illness was included for the study. Smoking history, simple

anthropometric data like height, weight, waist circumference were obtained according to the standard procedure of measurement. We started awareness program in the selected areas by doing sensitization camp at every 2-3 months. This has been done with the help of Rural Extension Centre, Viswa Bharati. Then a simple questionnaire was administered for assessing the awareness about metabolic health especially those related to diabetes and thyroid problems. A composite scoring was done for overall analysis of awareness. The persons were explained about the study and only those who gave informed written consent had been included in the final study. Continued consecutive samples were collected from ST population from areas with high density of tribal population under the coverage of Rural Extension Centre, Viswa Bharati. Non-tribal population (non-ST) from the same or neighborhood areas were also selected. Thus 406 individuals including all ethnicity/caste were included in the study to make an appropriate representation of rural West Bengal. The sample size was chosen on the basis of available resources.

Height (to ±0.1 cm) was measured using a wall-mounted stadiometer. The subject stood straight, with feet placed together and flat on the ground, heels, buttocks and scapulae against the vertical backboard, and arms loose and relaxed with the palms facing medially. The head was carefully positioned in the Frankfurt plane, with the lower margins of the orbit in the same horizontal plane as the upper margin of the external auditory meatus. Body weight (to ± 0.1kg) was measured using an electronic calibrated scale. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Blood sample for biochemical tests e.g. fasting plasma glucose (FPG), HbA1c, Fasting Serum insulin, Creatinine, Lipid profile, Uric acid, ALT, AST, Alkaline phosphatase (ALP) Free T4, TSH, Anti TPO antibody, Calcium, Phosphate, intact parathyroid hormone (iPTH), and 25 hydroxy Vitamin D (25OH D) was collected. The samples were analyzed using standard laboratory procedure. Diabetes was defined as per standard diagnostic criteria[2] satisfying either Fasting plasma glucose or HbA1c (Single measurement).The presence of metabolic syndrome was ascertained using the International Diabetic Federation (IDF) criteria[3].

Clearance from the Institutional Ethics Committee was obtained. The statistical analyses were performed with SPSS Statistics for Mackintosh, Version 21.0. Armonk, NY: IBM Corp. Chi-squared test was used to compare the categorical data and unpaired Student T test was used to compare the continuous variables.

Results

Four hundred fifty persons were screened. Complete data were available 406 individuals. Among them, 206 were STs and 200 belonged to the other casts.

Mean age was not significantly different between the groups. Male : female ratio was similar in both the groups (Table 1).

Both systolic and diastolic BP were similar in STs than non-STs. Among auxologic parameters, mean BMI was significantly lower in STs in comparison to non-STs. The waist circumferencewas also significantly lower in STs in comparison to non-STs (Table 1). When BMI of ≥25 was used to define obesity, 15% of STs and 36% of non-STs were found to be obese. When obesity and overweight were considered together (BMI ≥23), 28% of STs and 53% of non-STs were found to be in this category. These differences were also statistically significant. Using waist circumference criteria for obesity (Male ≥90 cm, Female ≥80 cm), 10% of ST males and 6% of ST females were found to be obese, whereas 33% of non-ST males and 63% of non-ST females were obese. As per IDF criteria, overall the prevalence of metabolic syndrome (MetS) was 22%. However, 34% of the non-tribes qualified for MetS as compared to only 8.5 % of the tribal cohort, p<0.001.

Overall prevalence of diabetes (known plus newly detected) was 8.3%. However, the prevalence was significantly lower in STs in comparison to non-STs (3.4% *versus* 15.2%). Both HbA1c and FPG were significantly lower in STs. HOMA-IR, a marker of insulin resistance was also lower in STs. Total cholesterol, LDL cholesterol, and triglyceride were significantly lower in STs. There was no significant difference in HDL cholesterol among the groups. ALT, AST, ALP and creatinine were similar in both the groups. Uric acid level was lower in STs (Table 2).

Mean 25OH D level was significantly higher in STs. However, calcium and iPTH levels were similar in both the groups.TSH and free T4 levels were also found to be similar among the groups.

Discussion

This study compared the metabolic and other related parameters between the STs and non-STs in the district of Birbhum, West Bengal, India. Birbhum district includes significant proportion of underdeveloped areas. A significant proportion of the population comprises of scheduled tribes (6.9%)[4]. We found that overall prevalence of MetS was significantly lower in STs in comparison to non-STs. This can be attributed by less consumption of processed food and more active lifestyle of the tribals[5]. Prevalence of obesity, as measured by BMI and waist circumference were significantly lower in STs. FPG, A1c, and insulin resistance as measured by HOMA were also significantly lower in STs possibly due to the same reason. Prevalence of diabetes is lower in STs. Dyslipidemia was

Table 1 — *Clinical parameters in ST and non-STs*

	ST	Non-ST	p
Age [Mean(SD)], Year	41.7(10.2)	42.6	0.126
Male : Female	0.65	0.79	0.385
BMI [Mean(SD)], kg/m^2	21.1(3.6)	23.6(4.0)	<0.001
Waist Circumference [Mean(SD)], cm	72.8(10.2)	81.3(12.0)	<0.001
SBP [Mean(SD)], mmHg	123.9(130)	125(11.8)	0.401
DBP [Mean(SD)], mmHg	79.8(7.1)	80.5(6.0)	0.35

Table 2 — *Biochemical parameters in In STs and non-STs*

	ST [Mean(SD)]	Non-ST [Mean(SD)]	p
FPG, mg/dL	103(25)	118(45)	<0.001
HbA1c, %	5.5(0.8)	5.9(1.4)	0.001
Total Cholesterol, mg/dL	165(36)	187(40)	<0.001
LDL Cholesterol, mg/dL	96(36)	117(30)	<0.001
HDL Cholesterol, mg/dL	47(12)	45(11)	0.147
Triglycerides, mg/dL	107(48)	143(73)	<0.001
Creatinine, mg/dL	0.92(0.68)	0.88(0.87)	0.427
Uric Acid, mg/dL	4.1(1.2)	4.4(1.3)	0.032
HOMA-IR	2.3(2.1)	3.2(1.9)	<0.001
ALT, mg/dL	45(22)	50(27)	0.058
AST, mg/dL	39(26)	31(17)	0.001
ALP, mg/dL	105(45)	108(28)	0.491
Calcium, mg/dL	9.7((0.6)	9.4(0.5)	0.56
Phosphorus, mg/dL	3.3(0.6)	3.2(0.5)	0.761
Vitamin D, ng/ml	20.8(8.1)	17.3(7.2)	<0.001
iPTH, pg/ml	64.6(50.6)	58.4(30.6)	0.170
FreeT4, ng/dl	1.06(0.2)	1.06(0.2)	0.991
TSH, mcg/ml	3.4(0.9)	5.2(0.9)	0.394

also lower in STs (lower Total and LDL cholesterol), although HDL level was similar. Uric acid, another marker of metabolic syndrome, was also lower in STs. Liver enzymes were similar in both the groups. Interestingly, vitamin D level was significantly higher in STs. This could be explained by more outdoor activities of tribal population. Higher vitamin D level in outdoor workers was also observed in northern part of India[6]. Yet unknown genetic polymorphism of vitamin D binding protein may also explain the difference[7,8]. However, other markers of bone metabolism like calcium, phosphorus, iPTH were similar in both the groups. There was no significant difference of TSH and Free T4 levels between STs and Non-STs.

Conclusion :

In the rural areas of district of Birbhum, prevalence of obesity, diabetes, dyslipidemia and metabolic syndrome was significantly lower in Scheduled tribes in comparison to non-Scheduled tribes.25 OH D level was significantly higher in tribal population.

Conflict of Interest : None

Acknowledgement

We sincerely acknowledge the fund received from The Department of Science and Technology, Government of West Bengal, India for this study.

References

1 Misra A, Khurana L — Obesity and the metabolic syndrome in developing countries. *Journal of Clinical Endocrinology and Metabolism* 2008; **93(Suppl 1):** S9-30. doi: 10.1210/jc.2008-1595.

2 Classification and Diagnosis of Diabetes. Diabetes Care [Internet].2016;39(Supplement 1):S13–22. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc16-S005

3 The IDF consensus worldwide definition of the metabolicsyndrome.http://www.pitt.edu/~super1/Metabolic/IDF1.pdf Accessed on 30.10.2019

4 https://www.census2011.co.in/data/religion/district/8-birbhum.html. Accessed on 30.10.2019

5 Guha S, Ismail M — Socio-Cultural Changes of Tribes and Their Impacts on Environment with Special Reference to Santhal in West Bengal 2015; **4(3):** 148-56.

6 Dharmshaktu P, Saha S, Kar P, Sreenivas V, Ramakrishnan L, Goswami R— Absence of vitamin D deficiency among common outdoor workers in Delhi. *Clin Endocrinol (Oxf)* 2019; **91(2):** 356-362. doi: 10.1111/cen.14012.

7 Newton DA, Baatz JE, Kindy MS, Gattoni-Celli S, Shary JR, Hollis BW, *et al* — Vitamin D binding protein polymorphisms significantly impact vitamin D status in children. *Pediatr Res [Internet]* 2019; Available from: https://doi.org/10.1038/s41390-019-0322-y

8 Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, *et al* — Vitamin D–Binding Protein and Vitamin D Status of Black Americans and White Americans. *N Engl J Med* 2013; **369(21):** 1991-2000.

(Continued from page 32)

et al — Development of the World Health Organization (WHO) Community Periodontal Index of Treatment Needs (CPITN). *Int Dent J* 1982; **32(3):** 281-91.

7 Emrich JL, Shlossman M, Genco JR — Periodontal disease in non-insulin dependent diabetes mellitus. *J Periodontol* 1991; **62(2):** 123-31.

8 Armitage GC — Clinical evaluation of periodontal diseases. *Periodontol 2000* 1995; **7(1):** 39-53.

9 Joss A, Adler R, Lang NP — Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. *J Clin Periodontol* 1994; **21(6):** 402-8.

10 Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE — Bleeding on probing. A predictor for the progression of periodontal disease? *J Clin Periodontol* 1986; **13(6):** 590-6.

11 Newman MG, Takei H, Klokkevold PR, Carranza FA — Carranza's clinical periodontology, 12th ed. Elsevier; 2001.

12 Yoneyama T, Okamoto H, Lindhe J, Socransky SS, Haffajee AD — Probing depth, attachment loss and gingival recession. *J Clin Periodontol* 1988; **15(9):** 581-91.

13 Health Canada. Report on the Findings of the Oral Health Component of the Canadian Health Measures Survey. 2007-2009. [Last accessed on 2014 Nov 07]. Available from: http://www.fptdwg.ca/assets/PDF/CHMS/CHMS-E-summ.pdf.

14 Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, *et al* — CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina Chapel Hill, USA). Prevalence of periodontitis in adults in the United States 2009 and 2010. *J Dent Res* 2012; **91(10):** 914-20.

15 Sheridan — Advances in dental research. *J Am Dent Asso* 1987; **115:** 741-2.

16 Casarin RC, Barbagallo A, Meulman T, Santos VR, Sallum EA, Nociti FH, *et al* — Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. *J Periodontal Res* 2013; **48(1):** 30-6.

17 American Diabetes Association — Standards of medical care in diabetes—2013. *Diab Care* 2013; **36 (Suppl 1):** S11-S66.

18 Costa FO, Miranda Cota LO, Pereira Lages EJ, Soares Dutra Oliveira AM, Dutra Oliveira PA, *et al* — Progression of periodontitis and tooth loss associated with glycemic control in individuals undergoing periodontal maintenance therapy: a 5-year follow-up study. *J Periodontol* 2013; **84(5):** 595-605.

Original Article

Management of gestational diabetes in a resource-limited setting in India

Debmalya Sanyal[1], Moutusi Raychaudhuri[2]

India has a huge burden of gestational diabetes mellitus (GDM) involving huge financial burden of monitoring and management, according to established guidelines.

We evaluated the effectiveness of a simple, safe and cost effective strategy of GDM management which can be easily implemented in resource-limited and remote areas. Medical nutrition therapy (MNT) was advised for two weeks after diagnosis of GDM. Patients were provided with free glucometers and were asked to self monitor blood glucose (SMBG) levels at fasting (FBG) and two hours post prandial (breakfast, lunch and dinner) once every week. Patients were asked to report every two weeks or at least once a month either in person or over phone/online with SMBG records. Treatment targets were a fasting glucose <95mg/dl and 2 hour postprandial glucose <120mg/dl. Regular or NPH human insulin was started according to prevailing SMBG reports if diet alone did not achieve control. 70 uncomplicated GDM patients were followed up till delivery and pregnancy outcomes were compared with 35 healthy pregnant controls.

In 98.6% of GDM patients adhered to our protocol. 20% were controlled on diet only. 90% of GDM patients on insulin required only regular insulin for glycaemic control with most requiring two doses of regular insulin-before breakfast and dinner. No case of macrosomia, perinatal death, birth injury, congenital malformations and shoulder dystocia were reported.

A simple, safe and cost-effective modification of established guidelines can be easily implemented in resource-limited and remote setting with excellent maternal and neonatal outcomes. Compliance with a simple strategy based on insulin and once weekly SMBG is effective in majority of uncomplicated GDM patients.

[*J Indian Med Assoc* 2019; **117(11):** 36-8]

Key words **: GDM, resource-limited and remote setting, insulin, SMBG, maternal and neonatal outcomes.**

Six million births in India is associated with prediabetes and diabetes, majority (90%) being are due to GDM[1]. In HAPO study even mild GDM was associated with adverse fetal, neonatal and pregnancy outcomes while ACHOIS and MFMUN trials showed that treating even mild GDM reduces perinatal morbidity[2-4]. Cornerstone of GDM management is glycemic control through lifestyle modification and proper monitoring; insulin is considered as the gold standard for glycemic control during pregnancy. Insulin is included in the national list of essential medicines in India, it is affordable and accessible. Effective self-management improves glycemic control and promotes better pregnancy outcomes in GDM[3,4]. The management of GDM is still challenging in remote and resource-limited areas in India due to the huge financial cost involved in monitoring and management of GDM according to established guidelines. Hence we evaluated the effectiveness of a simple, safe, cost effective and easily implementable approach for resource-constrained and remote settings.

[1]DM (Endocrinology), Professor, Department of Endocrinology, KPC Medical College, Kolkata 700032

[2]DM (Endocrinology), Professor, Endocrinology Unit, Institute of Child Health, Kolkata 700017 and Corresponding Author

Materials and Methods

The study was conducted in the Endocrine OPD of a medical college in Kolkata, India with patients referred from primary health centres (PHCs) from remote rural areas. 70 uncomplicated GDM patients were followed up till delivery & pregnancy outcomes were compared with 35 healthy pregnant controls. International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were used to diagnose GDM with fasting glucose ≥92 mg/dl, 1-hr glucose ≥180 mg/dl, 2-hr glucose ≥153mg/dl. Those with diagnosed pregestational diabetes were excluded.

Treatment targets of capillary SMBG were based on IADPSG guidelines with fasting glucose ≤95 mg/dl and 2 hour post meal glucose ≤120mg/dl. MNT was advised for two weeks after diagnosis of GDM. Regular or NPH human insulin was started according to prevailing SMBG reports if diet alone did not achieve targets.

Monitoring : Patients were provided with free glucometers and were asked to do four SMBGs once every week - fasting and two hour post prandial (breakfast, lunch

and dinner). Patients/family members were asked to report every two weeks or at least once a month either in person or over phone/online with SMBG records.

Pregnancy outcomes were compared between GDM and non-GDM groups using unpaired Student's t-test and Chi-square tests.

Results : Adherence to our protocol was 98.6% (69 patients). 20% (14 patients) were controlled on diet alone. 78.6% (55 patients) required insulin. 90.9% (50 patients) of those on insulin achieved target FBG without NPH insulin (only 5 required NPH insulin). 25.45% (14 patients) required regular insulin only once before breakfast, 50.9% (28 patients) required two doses before breakfast and dinner and 14.5% (8 patients) required three doses before each meal. No case of macrosomia , perinatal death, birth injury, congenital malformations and shoulder dystocia were recorded. Only 3 episodes of hypoglycemia GDM occurred in the GDM patients, none were severe. GDM pregnancy had significantly ($p < 0.05$) higher incidence of planned Caesarean Section (CS) delivery at term in 71% (49 patients) compared to 40% (14 patients) in non-GDM pregnancy. 20 patients (41%) of GDM pregnancy had planned CS on patient request compared to only 2 patients (14.3%) in non-GDM pregnancy (Table 1).

Table 1 — *Comparison of GDM and non-GDM pregnancies*

Outcome	GDM (n=69)	Non-GDM(n=35)	p-Value
Age of mothers (years)	26 ± 3.6	24 ± 4.8	Not significant
Pregestational BMI	23.5 ± 4.5	22.1 ± 3.2	Not significant
Birth Weight (g)	2814 ± 325	2695 ± 291	Not significant
Neonatal Hypoglycemia	2 (2.9%)	1 (2.85%)	Not significant
APGAR – 5min	10	10	Not significant
Preterm delivery	8(11.6%)	4(11.4%)	Not significant
Planned CS	49 (71%)	14(40%)	p <0.05
CS on patient request	20 (41%)	2 (14.3%)	p <0.05

Discussion

Successful outcome in GDM depends on the glycemic control maintained with meal plan or pharmacological intervention. Self Monitoring of Blood Glucose (SMBG) is an integral part of gestational diabetes mellitus (GDM) management. It improves glycemic control of GDM and feedback on self-management[5]. There is a consensus that measuring postprandial glucose levels is more important than pre-prandial levels since the former correlates better with adverse fetal and neonatal adverse events[6]. However it has been debated as to whether glucose should be measured 1 or 2 hours after a meal. Continuous glucose monitoring system (CGMS) has recently shown that glucose peaks occur about 70 ± 13 min after meals in nondiabetic pregnant women and after about 90 min in diabetic women[7]. Studies suggest different time intervals like 1, 1.5 and 2-hour post-meal for monitoring glycemic control[8]. FPG less than 95mg/dl, 1 hour PPG less than 140mg/dl or 2 hour PPG less than 120mg/dl is the IADPSG criteria for glycemic control is adequate to prevent macrosomia and adverse fetal outcome. In our study we went for a fasting of less than 95mg/dl and 2-hour postmeal values because of familiarity of clinicians with 2 hour postmeal value for diagnosis and monitoring of both diabetes and GDM. This approach was also in accordance with the Indian Diabetes In Pregnancy Study Group India (DIPSI) guidelines[9].

Daily SMBG has been the standard for women with GDM, however, new research has shown that SMBG testing every other day or every third day would not delay therapy modification in mild GDM[10]. We improvised further and went for SMBG once a week only, as cost, whether out of pocket or limited government resources, is the most important barrier to successful GDM management. Once weekly monitoring cuts down the cost of glucose strips in resource-limited setting. Moreover, simpler protocol is easier to follow decreases dropout rate and improves adherence, which was 98.6% in our study.

If after two weeks of MNT, SMBG criteria of glycemic control were not achieved we started our patient on insulin as recommended by most guidelines[11]. Studies suggest that 70% of GDM patients are controlled with MNT, however, in our study it was only 20%[12]. Cultural habits and myths in India such as, exercise is not good for pregnancy outcome and mother should eat for two have a profound negative impact on GDM patients. Sedentary habits and consumption of high calorie diet inspite of advice to the contrary could have led to failure of MNT in 80% of patients in present study.

We used only insulin and did not use metformin as it was not approved at the time of our study Moreover metformin is a category B medication in pregnancy with very high maternal-to-fetal transfer rate[13]. Neonatal hypoglycemia is not increased but premature delivery is slightly increased with metformin, moreover follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in offspring exposed to Metformin[14,15]. Further study of long term outcomes in the offspring is needed[16].

Insulin is the treatment of choice in GDM as it does not cross the placenta and at the same time achieves good glycemic control without any teratogenic effects. The glycemic control achieved with Regular and NPH insulins is comparable with analogue insulins, though analogues have slightly lower hypoglycaemia[17]. In our study, we used Regular and NPH insulins with very good outcome with only 3 episodes of mild to moderate hypoglycemia, reaffirming its cost-effectiveness in resource limited settings.

True to the fact that GDM is largely a post-prandial

hyperglycemia, 89.9% of our patients required only prandial insulins for glycaemic control with only 9.1% needing additional NPH insulin for fasting hyperglycemia. 25.48% required only once daily prandial insulin at breakfast, majority 50.9% needed twice daily insulin before breakfast and dinner and only 14.5% needed thrice daily prandial insulin to reach the targets. There was no statistically significant difference outcome measures, like birth weight, macrosomia, neonatal hypoglycemia pre-term delivery, perinatal death, birth injury or shoulder dystocia, between babies of healthy pregnant controls and GDM mothers.

The maternal outcome in GDM pregnancy was again similar to that in non-GDM pregnancy except that the elective caesarean section (CS) rate was significantly higher (71%) in GDM compared to 40% in non GDM group. There is background fear and anxiety among treating obstetrician and GDM patient regarding adverse outcomes and perinatal mortality with normal delivery in GDM pregnancy. In GDM group, 41% of planned Caesar were on patient request as opposed to 14.3% in non GDM group. Absence of hypertension and obesity coupled with lifestyle modification and a good level of glycemic control with adherence to our simple SMBG protocol are the probable reasons for these good outcome measures.

Our study had several limitations. It was neither blinded nor adequately powered. Moreover, our protocol was only intended for those patients with uncomplicated GDM. RCTs and adequately powered studies are needed to validate our approach.

Conclusion :

It is difficult to implement standard GDM guidelines in resource-constrained areas in developing country like ours. A simple and cost-effective easily implementable protocol is very important for good compliance and success of any GDM management protocol. Compliance with a simple strategy based on insulin and once weekly SMBG is effective in the majority of uncomplicated GDM patients in remote settings and resource-limited settings and ensures excellent maternal and neonatal outcomes .

Source(s) of support : NIL

Conflicting Interest (If present, give more details) : NIL

Acknowledgement : NIL

References

1 Mahalakshmi MM, Bhavadharini B, Maheswari K, Anjana RM, Jebarani S, Ninov L, *et al* — Current practices in the diagnosis and management of gestational diabetes mellitus in India (WINGS-5). *Indian J Endocrinol Metab* 2016; **20(3):** 364-8. doi:10.4103/2230-8210.180001

2 HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, *et al* — The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358(19):** 1991-2002.

3 Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS — Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; **352(24):** 2477-86.

4 Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, *et al* — A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; **361(14):** 1339-48

5 Franz MJ, Evert A — American Diabetes Association Guide to Nutrition Therapy for Diabetes. 2nd ed. Alexandria, VA: American Diabetes Association; 2012.

6 De Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, *et al* — Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 1995; **333(19):** 1237-41.

7 Ben-Haroush A, Yogev Y, Chen R, Rosen B, Hod M, Langer O — The postprandial glucose profile in the diabetic pregnancy. *Am J Obstet Gynecol* 2004; **191(2):** 576-81.

8 Buhling KJ, Winkel T, Wolf C — Optimal timing for post-prandial glucose measurement in pregnant women with diabetes and a nondiabetic pregnant population evaluated by the continuous glucose monitoring system (CGMS). *J Perinat Med* 2005; **33(2):** 125-31.

9 Seshiah V, Das AK, Balaji V, Joshi SR, Parikh MN, Gupta S — Diabetes in pregnancy study group. Gestational diabetes mellitus – guidelines. *J Assoc Physicians India* 2006; **54:** 622-8.

10 Mendez-Figueroa H, Daley J, Lopes VV, Coustan DR — Comparing daily versus less frequent blood glucose monitoring in patients with mild gestational diabetes. *J Matern Fetal Neonatal Med* 2013; **26(13):** 1268-72.

11 American Diabetes Association. Medical Management of Pregnancy Complicated by Diabetes. 5th ed. Alexandria, Virginia: American Diabetes Association; 2013.

12 ADA Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes 2019. *Diabetes Care* 2019; **42(Suppl 1):** S165–S172 .

13 Kovo M, Haroutiunian S, Feldman N, Hoffman A, Glezerman M — Determination of metformin transfer across the human placenta using a dually perfused ex vivo placental cotyledon model. *Eur J Obstet Gynecol Reprod Biol* 2008; **136(1):** 29-33

14 Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L — Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril* 2002; **77(3):** 520-5.

15 Hanem LGE, Stridsklev S, J ´ ul´ iusson PB — Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs. *J Clin Endocrinol Metab* 2018; **103:** 1612-21 55. Vanky E, Stridsklev S

16 Rowan JA, Rush EC, Plank LD — Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. *BMJ Open Diabetes Res Care* 2018; **6:** e000456.

17 Nicholson WK, Wilson LM, Witkop CT — Therapeutic management, delivery, and postpartum risk assessment and screening in gestational diabetes.*Evid Rep Technol Assess (Full Rep)* 2008.

Case Report

Cobblestone Lissencephaly with Polydactyly, Anterior Uveitis and Single Palmar Crease in two brothers — A case report

Jasodhara Chaudhuri[1], Tarun Kumar Samanta[2], Moumita Ghosh[3], Swapna Chakraborty[4]

The term "lissencephaly" refers to smooth brain points to a group of rare malformations that share the absence of normal cerebral convolutions. It leads to severely disabling conditions and seizures. There are several types of lissencephaly and on the basis of a classification based on etiologies and morphology five major groups of lissencephalies are identified of which cobblestone lissencephaly also known as type 2 lissencephaly is atypical. This group includes Walker-Warburg syndrome, Fukuyama Congenital Muscular Dystrophy and Muscle-Eye-Brain disease. We present an unreported form of syndromic type 2 lissencephaly with global developmental delay, generalized tonic clonic seizures, polydactyly, single palmer crease, anterior uveitis but with no features of muscle dystrophy in two brothers born of parents with non-consanguineous marriage.

[*J Indian Med Assoc* 2019; **117(11)**: 39-40]

Key words **: Lissencephaly, Cobblestone Lissencephaly, Walker-Warburg Syndrome, Fukuyama Congenital Muscular Dystrophy, Muscle-Eye-Brain disease.**

Cobblestone lissencephaly results from abnormal organogenesis of the brain and particularly of the glia limitans, which leads to complex neuronal migration disorders[1,2]. Cobblestone lissencephalies are characterized by a granular surface of the brain aspect associated with shallow sulci, abnormal myelination of the white matter, enlarged ventricles, brainstem and cerebellar hypoplasia. In contrast with classic lissencephalies brain is typically lined by a neuroglial layer. The most common form is associated with hydrocephaly(H), agyria(A), retinal dysplasia (RD) with or without encephalocoele(E). All these features are part of Walker-Warburg syndrome also known as HARD(E) which is usually lethal within first few months of life. Type 2 lissencephalies also include Fykuyama Congenital Muscular Dystrophy marked by a mutation in fukutin on 9q31 and Muscle-Eye-Brain disease caused by mutation in POMGNT 1 gene on 1p34-p33. These diseases are very rare and reliable population data to estimate incidence at birth is not available[3] (Fig 1).

Fig 1 — Patients with Parents

Case Report

Case 1 : An eleven year old male presented with global developmental delay, seizure disorder, polydactyly (one digit extra in all four limbs), single palmer crease, crowding of teeth, left sided anterior uveitis. Born with an uneventful perinatal history, he was apparently well till 7 months of age when one day the parents noticed that he was having "fits" which was like generalized tonic clonic seizures. He was prescribed antiepileptics which he is continuing. He had 2 episodes of breakthrough seizures. He attained head control at 8 months of age, learnt to sit at 6 years of age, learnt to stand at 9 years of age and learnt to walk at 10 years of age. He can only shout "ma", "ba" and nothing else. He recognizes his parents but cannot see properly and goes on picking aimlessly (Figs 2&3).

Examinations — On clinical examination he had microcephaly (HC 47 cm), flat facies, haziness in the media of left eye, polydactyly, single palmar crease. Slow writhing movements of the hands were present. The child had generalized wasting falling under Grade 4 Protein Energy Malnutrition (PEM).

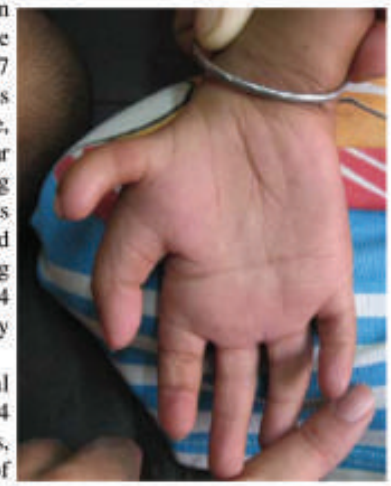


Fig 2 — Polydectyly with single Palmar Crease

On neurological examination, Grade 4 power in all four limbs, athetotic movement of both the hands, nystagmus and diminished tendon reflexes. IQ evaluation showed profound mental retardation. Opthalmological examination showed left sided anterior uveitis, high myopia and normal optic disc and macula. Serum CPK was normal. MRI of the brain showed diffuse symmetrical T2 and Fluid Attenuated Inversion Recovery (FLAIR) hyperintensities involving periventricular deep white matter

Department of Paediatric Medicine, Medical College and Hospitals, Kolkata 700073

[1]MBBS, MD, Postgraduate Trainee of Paediatric Medicine

[2]MBBS, DGO, DCH, MD (Paediatric Medicine), RMO *cum* Clinical Tutor and Corresponding Author

[3]MBBS, MD (Paediatric Medicine), previously Senior Resident. At present : RMO *cum* Clinical Tutor

[4]MBBS, DCH, MD (Paediatric Medicine), Professor & Head

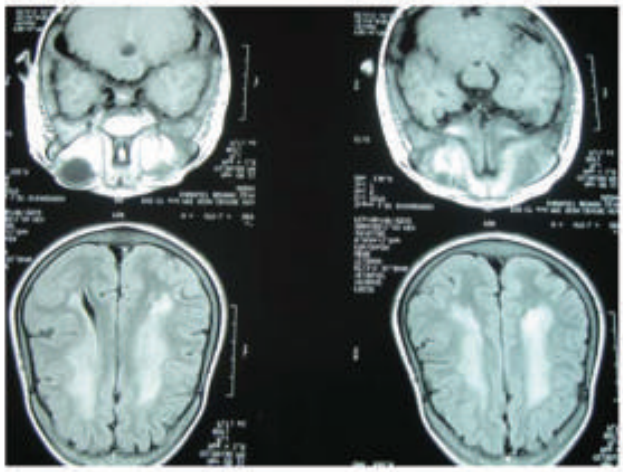


Fig 3 — MRI Brain of the older brother

of the frontoparietal lobes and pachygyria bilaterally with relative sparing of subcortical U-fibres and parieto-occipital and temporal lobes. There were tiny bilateral cerebellar cysts with hypoplasia of vermis, all suggestive of type II lissencephaly with level of confidence 10/10 (Fig 3). Muscle biopsy was normal. Brainstem Evoked Response Audiometry (BERA) was done and found to be normal and no metabolic abnormality was present.

Case 2 :

The six year old brother of the previous patient presented with exactly same findings and uneventful perinatal history. He was apparently well till 1 year of age when he started having convulsions in same manner. This child however has not achieved head holding as yet, cannot sit or do anything. He cannot speak and always stares vacantly. His investigation reports were similar to his brothers' from all aspects (Fig 4).

Examinations — Based on the history, clinical examination and investigations, the clinical features of the two brothers cannot be attributed to any of the three syndromes associated with lissencephaly type 2. The family was advised that the brothers should undergo further genetic analysis but that was not possible due to financial reasons. The parents apart from these two brothers have another child who is 8 year old male and is apparently normal till now with normal mental ability as he goes to a normal school and studies in a class appropriate for his age.

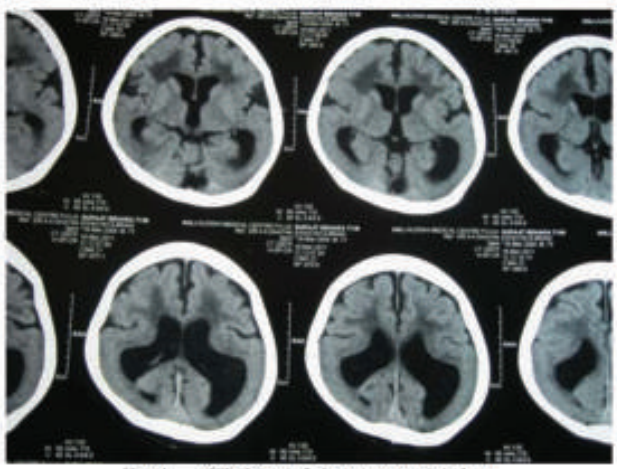


Fig 4 — CT Scan of the younger brother

Discussion

The lissencephaly syndromes associated with abnormal cortical lamination and are medically categorized as neuronal migration defects. Type 2 lissencephaly or cobblestone lissencephaly the cortex is unlayered. Type 2 lissencephaly is associated with 3 syndromes- Walker Warburg syndrome, Fukuyama congenital muscular dystrophy and Muscle-eye-brain disease[4]. The features of the three are the following (Table 1).

Table 1 — *differentiating features of the 3 congenital muscular dystrophies under lissencephaly type 2*

Features	WWS*	MEB**	FCMD***
Distribution	Worldwide	Finland	Japan
Severity	Most severe	Moderate	Less severe
Ocular feature	Anterior chamber malformation, retinal dysplasia	High myopia, cataract	cataract
Hydrocephalous	Common	Uncommon	Uncommon
Brainstem involvement	Common	Uncommon	Uncommon
Cerebral cortex	Type 2 lissencephaly	Type 2 lissencephaly	Type 2 lissencephaly
Hypotonia	Generalised	Generalised	Generalised
Cerebellar involvement	Cysts	Vermis hypoplasia[5]	Uncommon
Dandy Walker malformation	Common	Uncommon	Uncommon

*WWS =Walker-Warburg Syndrome
**MEB=Muscle-Eye-Brain disease
***FCMD=Fukuyama Congenital Muscular Dystrophy

Since the clinical spectrum of the two brothers do not match with any of the three syndromes associated with lissencephaly type 2, it may be a new syndrome associated with lissencephaly type 2 that is yet to be explored. No previous case report of such a syndrome is available anywhere.

Treatment options : Primarily supportive, including physical exercise and stretching activities. Genetic counseling should be offered to the parents.

Source of support : Nil

Conflict of interest : Nil

References

1 Dobyns WB, Leventer RJ — Lissencephaly: the clinical and molecular genetic basis of diffuse malformations of neuronal migration, PG Barth, ed. Mac Keith press, London. *International Review of Child Neurology series* 2003; 24-57.

2 Kato M, Dobyns WB — Lissencephaly and the molecular basis of neuronal migration. *Hum Mol Genet* 2003, **1:** R89-96.

3 Torres FR, Montenegro MA, Marques-De-Faria AP, Guerreiro MM, Cendes F, Lopes-Cendes I — Mutation screening in a cohort of patients with lissencephaly and band heterotopia. *Neurology* 2004; **62:** 799-802.

4 Taniguchi K, Kobayashi K, Saito K, Yamanouchi H, Ohnuma A, Hayashi YK, *et al* — Worldwide distribution and broader clinical spectrum of muscle-eye-brain disease. *Hum Mol Genet* 2003; **12(5):** 527-34.

5 Jissendi –Tchofo P, Kara S, Barkovich AJ — Midbrain-hindbrain involvement in lissencephalies. *Neurology* 2009; **72(5):** 410-8. doi: 10.1212/01.wnl.0000333256.74903.94. Epub 2008 Nov 19.

Drug Trial Report

Tamsulosin : Auroselective Alpha Receptor Blocker for treatment of Benign Prostatic Hyperplasia

Apul Goel[1]

Tamsulosin clearly offers advantages over other a1-adrenoceptor antagonists in terms of the need for a single daily dose only, and its low potential for hypotensive effects or interference with concomitant antihypertensive therapy. Dosage titration at the start of treatment is not necessary for the tamsulosin. Tamsulosin has a rapid onset of action and is effective in patients with moderate as well as severe symptoms. In combination with dutasteride, tamsulosin provides significantly greater benefit in men with moderate-to-severe LUTS associated with BPH.

[*J Indian Med Assoc* 2019; **117(11):** 41-4]

Key words **: Benign Prostatic Hyperplasia, Bladder Outlet Obstruction, Benign Prostatic Enlargement**

Benign prostatic hyperplasia (BPH) is a common problem faced by aging menthat negatively impacts quality of life. BPH is histologically characterized as an increase in the total number of stromal and glandular epithelial cells within the transition zone of the prostate gland. This hyperplasia causes the non-malignant, overgrowth of the prostate gland[1].

With advancing age, the force of urinary stream decreases. One important reason for this decline in force of the urinary stream is Bladder Outlet Obstruction (BOO) arising directly from Benign Prostatic Enlargement (BPE). This leads to Lower Urinary Tract Symptoms (LUTS), impaired bladder emptying (post-void residual urine), and predisposes to urinary tract infection. Fig 1 depicts the clinical manifestation of the BPH[1].

BPH is the fourth most prevalent disease in men aged >50 years. About 60% of men aged >50 years have histologic evidence of BPH. The prevalence progressively increases in men aged ≥70 years to 80%[2].

The pathogenesis of BPH is not yet fully understood. Several mechanisms are proposed to be involved in the development and progression of BPH. Although aging represents the central mechanism, recent novel findings also highlighted the key role of metabolic syndrome, systemic and local hormonal and vascular alterations, as well as prostatic inflammation that stimulates cellular proliferationasthe important mechanism involved in the development and progression of the BPH (Fig 2). An unknown stimulus would initiate inflammation that would create a pro-inflammatory environment within the prostate. BPH patients with Metabolic Syndrome have higher prostate growth rate and larger prostate volume[3].

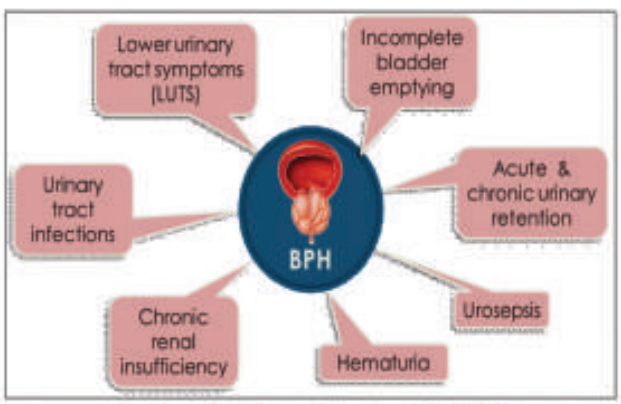


Fig 1 — Clinical manifestation of the BPH

[1]MBBS, MS (Surgery), MCh (Urology), DNB (Urology), Professor, Department of Urology, King George Medical University, Lucknow 226003 and Corresponding author

Management of BPH :

Target indications for treating BPH include reversing existing signs and symptoms of the disease or preventing the progression of the disease (Table 1)[1].

Management of BPH involves a cascade from watchful waiting, self-management, medical therapy, and surgical therapy (Fig 3).

Current therapeutic strategies for the treatment of LUST/BPH include alpha-blockers, 5-α reductase inhibitors, phosphodiesterase-5 (PDE-5) inhibitors, and anticholinergics. Among these therapeutic options, alpha-1 blockers are the first line of treatment for BPH. Tamsulosin, doxazosin, terazosin, alfuzosin and silodosinare the long-acting alpha-1 blockers approved for the treatment of BPH[1].

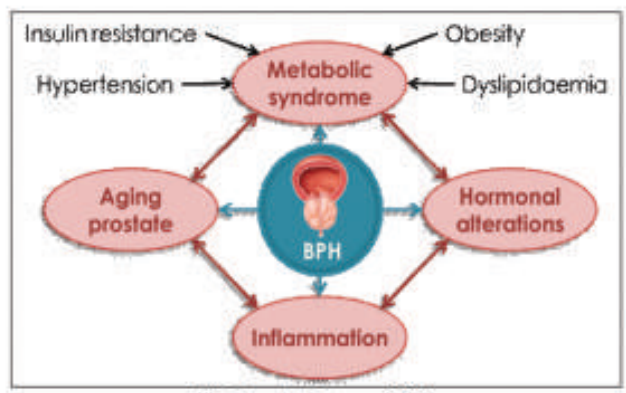


Fig 2 — Aetiology of BPH

Table 1 — *Rationale for treatment of BPH*

- To improveLUTS
- Eliminating hematuria secondary to BPH
- Improving bladder emptying
- Reversing acute urinary retention
- Preventing LUTS progression
- Preventing the development of acute urinary retention

Fig 3 — Cascade of BPH management

Tamsulosin for Treatment of BPH :

Pharmacodynamic properties and mechanism of action of tamsulosin —

Functional studies showed that a1 adrenoceptor subtype predominates in the prostate gland, prostatic capsule, prostatic urethra, and trigone. These receptors mediatebladder neck/prostatic muscle contraction. On the contrary, relaxation of the prostate smooth muscle improves urine flow and causes improvement in symptoms of LUTS in men with BPH (Fig 4). Tamsulosin is third-generation uro-selective a1A adrenergic receptor blocker indicated for the treatment of LUTS associated with BPH (LUTS/BPH)[4,5].

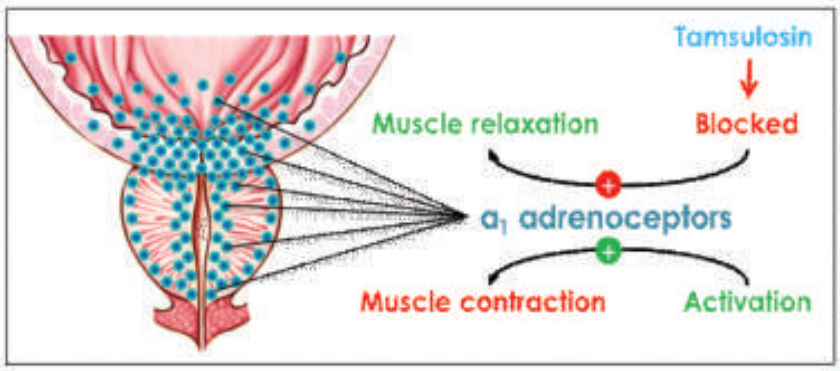


Fig 4 — Mechanism of action of Tamsulosin

Tamsulosin is generally well tolerated. Tamsulosin is associated with a lower potential for cardiovascular adverse effects[3].

Dosage of tamsulosin in BPH —

The starting dosage of tamsulosin for BPH management is 0.4 mg once daily orally with food. The dosage can be increased to 0.8 mg once daily in patients who fail to respond to the 0.4 mg dose after 2-4 weeks of administration[4].

Dosage adjustments are not required on the basis of age or mild to moderate hepatic impairment/renal dysfunction[3].

Tamsulosin in combination with dutasteride for treatment of BPH —

Dutasteride is a 5α- reductase inhibitor. Treatment with 5-α reductase inhibitors suppresses the dihydrotestosterone (DHT) levels, which lead to the induced apoptosis of prostatic cells that reduces prostate volume. Dutasteride reduces serum DHT levels by 95%, leading to a reduction of approximately 94-97% of DHT levels in the prostate. The rationale behind the combined use of tamsulosin with dutasteride to control BPH-related LUTS relies on the potential synergistic effect due to their different modes of action[6]. Treatment with tamsulosin and dutasteride combination provides significantly greater benefit in men with moderate-to-severe LUTSassociated with BPH and prostatic enlargement (usually greater than 40-ml)[7].

Clinical Efficacy and Safety of Tamsulosin for Management of BPH :

Efficacy and Safety of Tamsulosin in Patients with LUTS Associated with BPH —

Objectives :

To evaluate the efficacy and safety of two once-daily doses (either 0.4 mg or 0.8 mg) of tamsulosin in patients with benign prostatic hyperplasia.

Methods :

This was a phase III, randomized, parallel-design, double-blind trial. A total of 756 patients with BPH were randomized to receive either tamsulosin (0.4 and 0.8 mg/day) or placebo. Primary efficacy parameters were improvement in the total American Urological Association symptom index (AUA-SI) score and peak urinary flow (Q_{max}).

Results :

- Statistically significant improvements in efficacy parameters were seen in tamsulosin-treated group compared with placebo-treated patients (Fig 5). They-axis showschange in AUA-SI score.
- The0.4-mg/day dose demonstrated a rapid onset of action (4 to 8 hours) based on Qmax after the first dose of double-blind medication.
- Excellent tolerance at 1-week after the initial 0.4-mg/day dose and continued

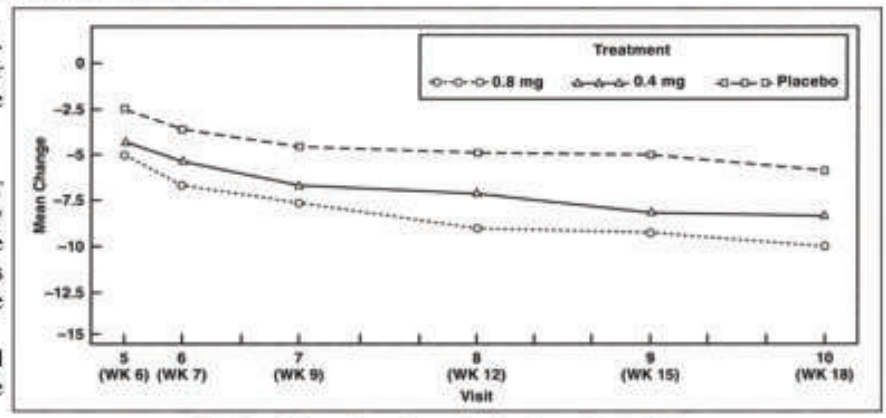


Fig 5 — Mean change from baseline in total AUA-SI score

tolerance during the additional 12 weeks of 0.4- and 0.8-mg/day dosing.

Conclusion :

Tamsulosin was effective and well-tolerated in men with BPH at both the 0.4 and 0.8 mg/day dose levels, without the blood-pressure-lowering effects[8].

Better Efficacy of Tamsulosin versus Terazosin in the Treatment of BPH —

Objectives :

To evaluate the efficacy and tolerability of tamsulosin versus terazosin in men with signs and symptoms of BPH.

Methods :

This was 11-week, randomized, open-label, multi-center, parallel-design study. A total of 1993 patients with BPH and moderate-to-severe LUTS were randomized to receive tamsulosin (0.4 mg/day) or terazosin (5 mg/day).

Results :

- Following the 4-days of treatment, the tamsulosin group demonstrated a clinically and statistically significant difference in total AUA-SI score in favor of tamsulosin.
- After 4-days of treatment, the adjusted mean changes in AUA-SI scores were –5.1 and –3.8 (P<0.001) for tamsulosin and terazosin treated patients, respectively (Fig 6).
- Secondary efficacy endpoint score comparisons also were statistically significant in favour of tamsulosin.
- Dizziness and somnolence were reported significantly more often (each, P<0.001) in the terazosin group than in the tamsulosin group. Tamsulosin was associated with fewer discontinuations due to adverse events.

Conclusions :

After 4-days of treatment with tamsulosin, reduction in BPH symptom severity was significantly greater than treatment with terazosin. This indicates a more rapid onset of clinical action of tamsulosin. Tamsulosin was well tolerated, with fewer adverse events associated with reduced blood pressure[9].

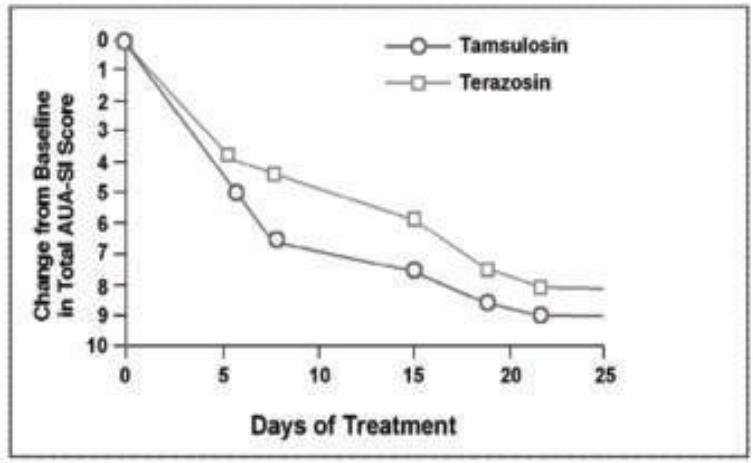


Fig 6 — Change from baseline in total AUA-SI score

Comparable Efficacy and Advantages of Tamsulosin over Alfuzosin —

Objectives :

To compare the efficacy and tolerability of the alpha-1-subtype selective drug tamsulosin with the non-subtype-selective agent alfuzosin in the treatment of patients with LUTS associated with BPH.

Methods :

This was a randomized, parallel-design, double-blind, randomized, parallel-design, double-blind phase III trial. A total of 256 patients with BPH and LUTS suggestive of BOO (symptomatic BPH) received tamsulosin 0.4 mg once daily or alfuzosin 2.5 mg three times daily for 12 weeks.

Results :

- Tamsulosin and alfuzosin produced comparable improvements in Qmax and total Boyarsky symptom score (Fig 7).
- Both treatments were well tolerated.
- Tamsulosin had no statistically significant effect on blood pressure,while alfuzosin induced a significant reduction in both standing and supine blood pressure, compared with baseline (P < 0.05).

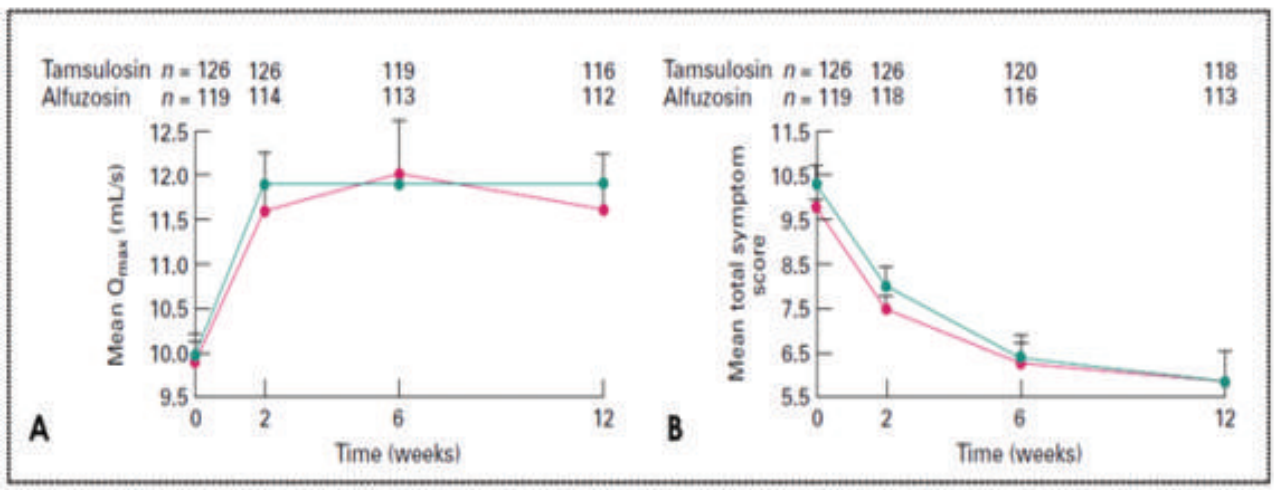


Fig 7 — (A) Mean maximum urinary flow rate. (B) Mean total Boyarsky symptom score (Green: Tamsulosin; Red: Alfuzosin)

Conclusion :

Tamsulosin, in contrast to other currently available alpha 1-adrenoceptor antagonists, can be administered without dose titration. Another advantage compared with alfuzosin is the once-daily dosing regimen of tamsulosin[10].

Tamsulosin in Combination with Dutasteride for Treatment of BPH: Combat study —

Objective :

To evaluate efficacy of combination therapy with tamsulosin and dutasteride in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression over 4 years in men at increased risk of progression.

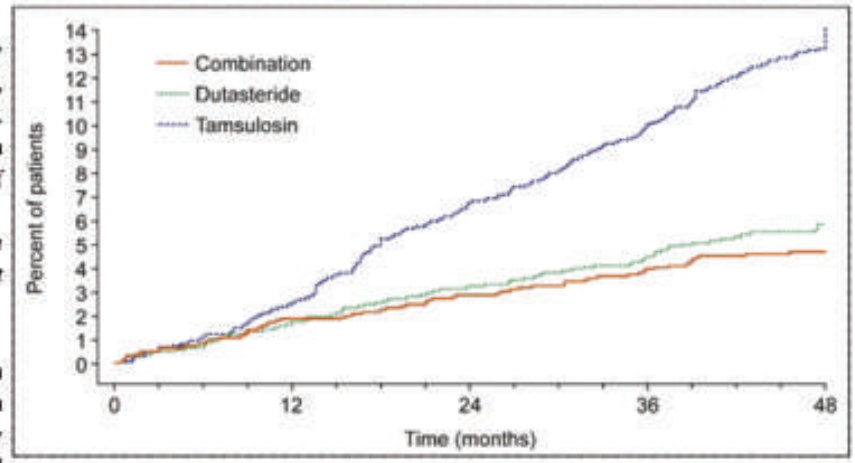


Fig 8 — Kaplan-Meier estimates of time to the first episode of acute urinary retention or benign prostatic hyperplasia-related prostatic surgery

Methods :

This was a 4-year, multicenter, randomized, double-blind, and parallel-group study. A total of 4844 men with a clinical diagnosis of BPH, International Prostate Symptom Score ≥12, prostate volume ≥30 cm^3, prostate-specific antigen 1.5-10 ng/ml, and maximum urinary flow rate (Q_{max}) >5 and ≤15 ml/s with minimum voided volume ≥125 ml.

Results :

- Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery.
- Combination therapy was also significantly reduced the relative risk of BPH clinical progression.
- Combination therapy provided significantly greater symptom benefit at 4 years.
- Safety and tolerability of combination therapy was consistent with previous experience with dutasteride and tamsulosin monotherapies.

Conclusions :

This study supported the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement[7].

References

1 Lepor H — Alpha blockers for the treatment of benign prostatic hyperplasia. *Reviews in Urology* 2007; **9(4):** 181

2 Abdollah F, Briganti A, Suardi N, Castiglione F, Gallina A, Capitanio U, *et al* — Metabolic syndrome and benign prostatic hyperplasia: evidence of a potential relationship, hypothesized etiology, and prevention. *Korean Journal of Urology* 2011; **52(8):** 507-16.

3 Briganti A, Capitanio U, Suardi N, Gallina A, Salonia A, Bianchi M, *et al* — Benign prostatic hyperplasia and its aetiologies. *European Urology Supplements* 2009; **8(13):** 865-71.

4 Prabhu GL, Prajapati H, Chaturvedi A, Dave N, Jain AB — Tamsulosin in urology: beyond benign prostatic hyperplasia. *Drugs & Therapy Perspectives* 2019; **35(4):** 181-4.

5 Dunn CJ, Matheson A, Faulds DM — Tamsulosin. Drugs & Aging 2002; **19(2):** 135-61.

6 Dimitropoulos K, Gravas S — Fixed-dose combination therapy with dutasteride and tamsulosin in the management of benign prostatic hyperplasia. *Therapeutic Advances in Urology* 2016; **8(1):** 19-28.

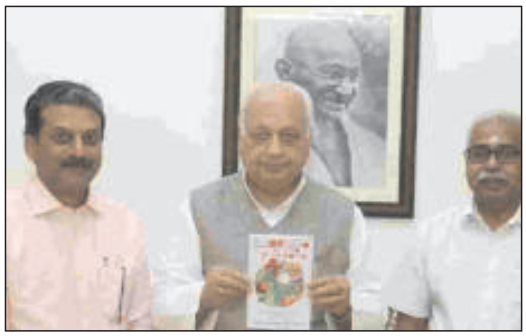
7 Roehrborn CG, Siami P, Barkin J, Damiao R, Major-Walker K, Nandy I, *et al* — CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *European Urology* 2010; **57(1):** 123-31.

8 Lepor H — Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. *Urology* 1998; **51(6):** 892-900.

9 Narayan P, O Leary MP, Davidai G — Early efficacy of tamsulosin versus terazosin in the treatment of men with benign prostatic hyperplasia: a randomized, open-label trial. *Journal of Applied Research in Clinical and Experimental Therapeutics* 2005; **5(2):** 237.

10 Narayan P, O Leary MP, Davidai G — Early efficacy of tamsulosin versus terazosin in the treatment of men with benign prostatic hyperplasia: a randomized, open-label trial. *Journal of Applied Research In Clinical and Experimental Therapeutics* 2005; **5(2):** 237.

222nd Meeting of Central Working Committee at Port Blair, A&N on 1-2 November, 2019



Hon Governer releasing the book (Good food to reverse Diabetes) by Dr Sreejith N Kumar

IMA Initiative 'Prevention of Diabetes Blindness'

Dr.Rajan Sharma,NPE at IMA Visakhapatnam

Dr. (Prof) Sivasankara Pillai felicitated by Nemom Branch

IMA Kannur Branch

62nd Annual State Conference of IMA Kerala

IMA UNESCO 'Bioethicon 2019' on 8-10 November, SRM Medical College, Chennai

NATCON 2019

94th NATIONAL CONFERENCE OF INDIAN MEDICAL ASSOCIATION
80th ANNUAL MEETING OF CENTRAL COUNCIL OF IMA
(Organised by Bengal State Branch, IMA)
Friday and Saturday, December 27-28, 2019, Biswa Bangla Convention Centre, New Town, Kolkata
Conference Secretariat: 53, Creek Row, Sir Nil Ratan Sircar Sarani, Kolkata-700014,Bengal, India
Tel.: +91-33-22893728 / 22497086 • **Website:** www.imanatcon2019.com • **Email:** imanatcon2019@gmail.com

Registration Form

Name: Prof/Dr./Mr./Ms._____ _____ _____
Surname Middle Name First Name

Designation _____

Mailing Address_____

City_____State _____Postal/Zip Code_____

Country _____ Phone (Off.) _____(Res.)_____

Fax_____Email Address _____

Accompanying Person(s) Name (1): _____
(2): _____

Amount details: GST details (optional): _____

Registration*: Self: Rs. _____, Accompanying Person(s): Rs. _____

Hotel **: Hotel Name: _____, Dates:Check-in: _____,Check-out: _____

Occupancy type (Pl. tick one): (S)ingle / (D)ouble / (T)win sharing, Accom. Expenses: Rs. _____

Total: Rs. _____Total (in words): Rupees _____

Payment details: NEFT: UTR No. _____, Dt.: _____ / Cheque/D.D. No. _____ dt. _____

* - Delegate Registration Fees (Taxes included): **(Delegate's Signature)**

Category	Till August 31, 2019	Till Sept 30, 2019	Till Nov. 30, 2019	Spot Registration (Cannot beguaranteed)
IMA Members	Rs. 2,360/-	Rs. 3,540/-	Rs. 4,130/-	Rs. 5,900/-
Non-IMA Members	Rs. 3,540/-	Rs. 4,130/-	Rs. 4,720/-	Rs. 5,900/-
Medical Students / P.G. / Junior Residents	Rs. 1,180/-	Rs. 1,770/-	Rs. 2,360/-	Rs. 3,540/-
Accompanying persons (Only participation in sessions and Meals, No delegate kit	Rs. 1,180/-	Rs. 1,770/-	Rs. 2,360/-	Rs. 3,540/-
International Delegates	USD 100	USD 125	USD 150	USD 200
Accompanying Persons (International delegates)	USD 75	USD 100	USD 125	USD 200

** - Hotels and charges (Taxes inclusive):

Hotel Name	Single Occupancy (INR)	Double Occupancy (INR)	Twin Sharing Basis (INR)
Westin, Kolkata	8000	10000	5000
Novotel Hotel and Residences, Kolkata	9000	10000	5000
Pride Plaza Hotel, Kolkata	6000	7000	3500
Holiday Inn, Kolkata	7000	8000	4000

For International delegates only:
Passport details (for Visas purposes): Name (as in passport): _____ No: _____

Issue date___/___/_____ Valid till ___/___/_____ Country of issue: _____

Dietary Requirements

Special dietary requirements for lunch:
I am non-vegetarian/vegetarian/Jain/other (please specify):_____

Special dietary requirements for Dinner:
I am non-vegetarian/vegetarian/Jain/other (please specify):_____

Completed registration form may kindly be sentto the Conference Secretariat as per details on the top of the form

Conference Secretariat:
Contact person in IMA Conference Secretariat:**Mr. Debabrata Chatterjee, Mobile No. +91-9874756756**

All payments to be made in the account of "NATCON 2019" payable by cash/ at par crossed cheque / DD / online transfer through NEFT (A/c Name: NATCON 2019, A/c. No. 3731920708, IFSC Code: CBIN0281041, Type of A/c.: Savings)
Account details for International transactions: - Account Name: Indian Medical Association-FCRA; Beneficiary Bank: Syndicate Bank; Beneficiary Account No: 90672010022569;Bank's Address: CR Building, IP Marg, New Delhi-110002; Beneficiary Bank SWIFT Code: SYNBINBB126; IFSC Code: SYNB0009067;Reference: 'NATCON 2019"

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

Date of Publication : 15th November, 2019

Registration No. KOL RMS / 476 / 2017-19

RNI Regd. No. 2557/1957
VOL. 63, NO. 11, November 2019, Kolkata

If not delivered please return to Journal of the IMA (JIMA) Sir Nilratan Sircar IMA House, 53 Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014

Printed and Published by Dr Sanjoy Banerjee on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata 700009, and Published from Sir Nilratan Sircar IMA House, 53 Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014. Editor : Dr Golokbihari Maji